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# Serotonin Transporter Gene Variation and its Association with Cognitive Vulnerability to Depression

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# Serotonin Transporter Gene Variation and its Association with Cognitive Vulnerability to Depression

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# Serotonin Transporter Gene Variation and its Association with Cognitive Vulnerability to Depression

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Depression is a serious condition that affects a significant proportion of the population and causes substantial life impairment (Kessler et al., 2003). Cognitive models of depression vulnerability (e.g., Teasdale, 1988) posit that information processing biases for negative and positive stimuli play a critical role in the disorder. Change in negative thinking in response to dysphoric moods is referred to as cognitive reactivity and has been shown to be a risk factor for future increases in depression (e.g., Beevers & Carver, 2003; Segal et al., 2006). Interestingly, recent behavioral genetics research indicates that certain genes may influence cognitive factors associated with depression. The short allele of a polymorphism of the serotonin transporter gene (5-HTTLPR) has been associated with increased risk for depression in the context of life stress (Caspi et al., 2003); however, the psychological mechanisms that increase depression risk for short 5-HTTLPR allele-carriers have not been definitively identified. Recent work has begun to reveal an association between the 5-HTTLPR and cognitive factors associated with depression such as attention bias for emotional information (Beevers et al., 2007) and negative thinking style (Hayden et al., 2007). A pilot study ($n$ = 156) revealed an association between 5-HTTLPR and cognitive reactivity for attention bias for happy faces. The current study ($n$ = 180) extended and improved upon the pilot study's methodology and examined the relationship between the 5-HTTLPR and cognitive reactivity for attention to sad and happy faces as well as cognitive reactivity for dysfunctional attitudes. Cognitive variables were assessed after a neutral mood induction and after a sad mood induction at two laboratory sessions separated by at least 24 hours. There was a significant association between the 5-HTTLPR and cognitive reactivity for attention bias for emotional faces among Caucasian participants. Specifically, the short allele was associated with increased bias for emotional faces after the sad mood induction

compared to the neutral mood induction. There was a linear relationship between number of short alleles possessed by participants and increase in bias for emotional information. The 5-HTTLPR was not significantly associated with cognitive reactivity for dysfunctional attitudes, but the effect was in the expected direction. Results are discussed in the context of recent neuroimaging research and plasticity models of behavior genetics. Implications for a model of depression vulnerability integrating genetic, neural, and cognitive factors and future directions for similar behavioral genetics studies are discussed.

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# Chapter 1: Background and Significance

## 1.1 Cognitive Models of Depression Vulnerability

### 1.1.1 Impact of Depression

Major depressive disorder (MDD) is a common and recurrent condition that has been estimated to affect approximately 16% of the population sometime in their life and has a 6.6% point prevalence over 12 months (Kessler, Berglund, Demler, Jin, Koretz, Merikangas, et al., 2003). MDD predicts poor mental, physical, emotional, and social functioning (Judd, Akiskal, Zeller, Paulus, Leon, Maser, et al., 2000; Wells & Sherbourne, 1999). In addition, MDD is one of the leading causes of world-wide disability (Murray & Lopez, 1997) and depression-related costs exceeded $80 billion in the United States in the year 2000 (Greenberg, Kessler, Birnbaum, Leong, Lowe, Berglund, et al., 2003). MDD is also strongly associated with suicide in the United States (Nock & Kessler, 2006) and cross-nationally (Nock, Borges, Bromet, Alonso, Angermeyer, Beautrais, et al., 2008).

Due to the individual, social, and economic costs of depression, it is important to understand the underlying factors that make individuals vulnerable to depression. Cognitive theories of vulnerability to depression (e.g., Beck, 1979; Teasdale, 1988) posit that underlying cognitive risk factors are activated in the context of life stress or a negative mood. Similarly, a polymorphism of the serotonin transporter gene (5-HTTLPR) has been shown to increase risk for depression in the context of life stress (Caspi, Sugden, Moffitt, Taylor, Craig, Harrington, et al., 2003). The current research explores the potential relationship between these two vulnerabilities to depression.

### 1.1.2 Beck's Cognitive Theory of Depression Vulnerability

Perhaps the leading cognitive theory of depression vulnerability was developed by Beck (e.g., Beck, 1979) and many other cognitive theories trace their roots at least partially to this model. Briefly, Beck's model proposes that individuals consolidate information received from the outside world into stable patterns (i.e., schemas) that they then use to help screen out, sort, code and store future information. All individuals develop schemas to help process the plethora of information encountered in daily life, but some develop schemas that negatively biased. For example, if early experiences are characterized by negative experiences, abuse, stress, or trauma, this may lead to negatively toned schemas. These negative schemas often contain a negative triad of dysfunctional attitudes about the self, the world, and the future. Furthermore, these schemas are thought to be absolutistic, global, and rigid.

According to Beck (1979), the presence of negative schemas does not by itself lead to depression. Rather, negative schemas often remain latent until they are activated by stress or negative life interactions. Thus, Beck's theory represents a diathesis-stress model whereby the schemas are the underlying diathesis, or vulnerability, that is activated by negative or stressful life events.

There is significant evidence to suggest that depression is characterized by the negative thinking proposed in Beck's model. A number of studies have demonstrated that individuals who are depressed display more negative attitudes than those who are not depressed (for a review, see Ingram, Miranda, & Segal, 1998), but this leaves the possibility that the negative attitudes are simply byproducts or symptoms of depression. Indeed, studies that evaluated cognitive vulnerability factors in depressed individuals and

then again when those individuals were in remission found that the cognitive factors disappeared with the remission of the depressive episode (e.g., Dobson & Shaw, 1987; Gotlib & Cane, 1987).

This led some to argue that the cognitive factors are not causally related to depression but rather are byproducts or correlates of depression (e.g., Barnett & Gotlib, 1988). Furthermore, early prospective tests of cognitive vulnerability failed to demonstrate a link between dysfunctional attitudes and the onset of depression. For example, in a large community study, Lewinsohn, Steinmetz, Larson, and Franklin (1981) demonstrated no differences in dysfunctional attitudes among those who became depressed and those who did not over a one year follow-up. A similar study found no differences between those who displayed depression-related schemas and those who did not in the development of depression over a four month period (Hammen, Marks, deMayo, & Mayol, 1985).

### 1.1.3 Teasdale's Differential Activation Hypothesis

Though the idea that cognitive vulnerability factors are latent until activated by some negative event is present in Beck's (1979) model, Teasdale (1988) refined this idea in his Differential Activation Hypothesis to help account for the large body of research failing to demonstrate differences in dysfunctional attitudes between previously depressed and never depressed individuals and the failure of dysfunctional attitudes to predict future depression. Essentially, the Differential Activation Hypothesis states that vulnerability to depression is "powerfully related to differences in patterns of thinking that are activated *in the depressed state*" (Teasdale, 1988, p. 251, emphasis original). Furthermore, the hypothesis predicts that a broad range of cognitive processes –

including memory, self perception, and information processing – will be affected and will be negatively biased in depression vulnerable individuals. The hypothesis does not specify what types of situations or events might lead to activation of negative information processing and dysfunctional attitudes; the key is that cognitive vulnerability factors will be most easily observed when individuals are depressed or in a negative mood. Any event that induces a negative mood would be considered sufficient for activating the cognitive vulnerability factors.

The Differential Activation Hypothesis argues that activation of cognitive vulnerability factors in a negative mood contributes to both the maintenance and onset of depressive episodes. For example, once a negative mood exists, it will activate negative information processing which will, in turn, result in further increased in negative mood as memory, attention, and interpretation of events are biased for negative information. According to the hypothesis, this then leads to a positive feedback loop where negative mood and negatively biased information processing are each reinforcing and increasing the other serving to worsen the negative mood. This can lead a simple negative mood to increase in severity into clinical depression and can reinforce the depressive episode once it has begun.

Obviously, not all individuals who experience a negative mood spiral into depression, so there must be individual differences in strength and duration of the activation of cognitive vulnerability factors in the context of a negative mood. The Differential Activation Hypothesis does not identify a specific factor that might contribute to these individual differences, but Teasdale (1988) acknowledges that these individual differences likely depend on environmental, psychological, and biological

factors. For example, social support or lack thereof may be an important environmental factor that affects the strength or duration of the activation of cognitive vulnerability factors in the context of a negative mood. Identifying and understanding the factors that contribute to increasing the strength and duration of negative information processing in a negative mood is important to build a better etiological model of depression vulnerability and will be discussed more below.

Regardless of why there are individual differences in the likelihood, strength, and duration of activation of cognitive vulnerability factors (e.g., dysfunctional attitudes, negatively biased information processing), the increase in these vulnerability factors when in a negative mood is the primary measure of vulnerability in the Differential Activation Hypothesis. Depression vulnerable and non-vulnerable individuals are expected to have similar levels of vulnerability factors when not in a negative mood, but vulnerable individuals will exhibit an increase in these factors when in a negative mood. An increase in cognitive vulnerability factors in response to a negative mood has been labeled *cognitive reactivity*.

### 1.1.4 Cognitive Reactivity and Depression Vulnerability

A growing body of research has examined the relationship between cognitive reactivity and vulnerability to depression conferred by a previous episode of depression. A majority of these studies have found greater cognitive reactivity among recovered depressed individuals than those who were never depressed. For example, Miranda and Persons (1988) found greater dysfunctional attitudes among women who had previously experienced an episode of depression compared to women who never had an episode of depression. However, this relationship was only observed after the women had

undergone a negative mood induction procedure. Miranda and colleagues replicated this finding using a sad film mood induction (Miranda, Gross, Persons, & Hahn, 1998). Van der Does (2002a) found that formerly depressed and never depressed individuals experienced similar levels of sadness after a negative mood induction, but the formerly depressed participants showed a significantly greater increase in dysfunctional attitudes. Miranda, Persons, and Nix Byers (1990) found the same relationship between dysfunctional attitudes and history of depression with naturally occurring mood. Similarly, Lewinsohn, Allen, Seely, and Gotlib (1999) found a stronger relationship between naturally occurring mood and dysfunctional attitudes among those with a history of depression compared to those without a history of depression.

Cognitive reactivity in depression vulnerable individuals has also been observed in information processing. For example, Hedlund and Rude (1995) found that, after completing a self-focus procedure, formerly depressed individuals unscrambled more negative sentences in a scrambled sentences task compared to individuals who were never depressed. Taylor and Ingram (1999) examined information processing in non-depressed children of currently depressed and never depressed mothers using a self-referent encoding task. They found that the children of depressed mothers (high risk) and children of non-depressed mothers (low risk) did not differ on information processing tasks when in a neutral mood; however, when induced into a negative mood, high risk children endorsed fewer positive adjectives as self descriptive than the low risk group and remembered significantly more negative adjectives rated as self descriptive. Similarly, Joormann, Talbot, and Gotlib (2007) found that girls of formerly depressed mothers

demonstrated increased bias for sad faces when in a sad mood compared to girls of never depressed mothers.

### 1.1.5 Cognitive Reactivity and Prospective Risk of Depression

While there have been some failures to replicate the relationship between depression history and cognitive reactivity to a negative mood (e.g., Brosse, Craighead, & Craighead, 1999), a majority of studies support the existence of the relationship between vulnerability and cognitive reactivity (for a review, see Scher, Ingram, & Segal, 2005). However, an important question remains: is greater cognitive reactivity to a negative mood predictive of future increases in depression? This question is important to answer to establish the temporal precedence of cognitive reactivity to depression and that cognitive reactivity is a risk factor for depression. The priming research using depression vulnerable populations established the relationship between the two but leaves open the possibility that cognitive reactivity is a consequence of a previous depressive episode, but it does not indicate that cognitive reactivity leads to future increases in depression. Therefore, longitudinal research examining cognitive reactivity is important in establishing its relationship to depression vulnerability.

There have been fewer longitudinal studies specifically examining cognitive reactivity in predicting future depressive symptoms. In a landmark study, Segal, Gemar, and Williams (1999) examined cognitive reactivity in formerly depressed patients treated either with psychotherapy or pharmacotherapy. The patients underwent a negative mood induction during which they listened to sad music and recalled a time in their life when they were sad. They were administered the dysfunctional attitudes scale (DAS) before and after the mood induction. Segal and colleagues found that patients who demonstrated

greater increases in dysfunctional attitudes after the negative mood induction were at a significantly greater risk for a depressive relapse over a period of several years than patients with lower cognitive reactivity.

Segal, Kennedy, Gemar, Hood, Pedersen, and Buis (2006) replicated these results using identical methods to Segal, Gemar, and Williams (1999). Remitted depressed patients were administered the DAS before and after a negative mood induction consisting of sad music and autobiographical recall of a sad event. The researchers found that patients who demonstrated a marked increase in dysfunctional attitudes following the sad mood induction were more likely to experience a relapse depressive episode over an 18-month follow-up than were patients who showed lower cognitive reactivity.

Cognitive reactivity in information processing has also been associated with risk for future increases in depression. For example, Beevers and Carver (2003) administered a negative mood induction to formerly depressed and never depressed college students. Before and after the mood induction, participants completed a computer-administered dot-probe task assessing attention for negative words. Beevers and Carver found that increases in attention bias for negative information after the negative mood induction interacted with life stress to predict increases in depressive symptoms seven weeks later. This result was found even when controlling for depression history, suggesting that the risk associated with cognitive reactivity cannot be solely attributed to vulnerability conferred by a previous depressive episode. These results are important because they suggest that cognitive vulnerability is a marker of risk that is independent of depression

history and can predict future increases in depressive symptoms even among never depressed individuals.

### 1.1.6 Genetic Risk and Cognitive Vulnerability to Depression

Many studies reviewed above operationalize vulnerability to depression as having previously experienced an episode of depression due to the fact that previous episodes confer considerable risk for future depressive episodes. However, this obviously provides an incomplete model of cognitive vulnerability to depression since it has limited ability to identify or explain factors that might lead to the initial episode of depression.

One potential vulnerability factor that has been garnering more interest and research over the last 30 years is genetic vulnerability. The earliest studies of genetic vulnerability to depression involved the study of twins and children adopted away from their biological family. So-called twin studies attempt to estimate the contribution of genetic effects of a disorder by examining the difference in concordance for the disorder between monozygotic (identical) and dizygotic (fraternal) twins. The adoption method compares disorders in children adopted away from their biological family to those raised with their biological family. Though these methods have flaws, if done rigorously, they can provide estimates of the genetic contribution to a disorder (see Plomin, DeFries, McClearn, & McGuffin, 2001, for a more detailed discussion of these methods and their limitations). A fairly recent meta-analysis of methodologically rigorous family, twin, and adoption studies yielded an odds ratio of 2.84 for major depression for a proband who had at least one first-degree relative with major depression and a heritability estimate of 31%-42% for major depression (Sullivan, Neale, & Kendler, 2000). A more recent study examining a very large (> 15,000) set of complete twin pairs found a heritability estimate

of 38% for major depression, replicating the results of the meta-analysis (Kendler, Gatz, Gardner, & Pedersen, 2006b). These studies indicate a moderate influence for genetic factors in major depression compared with environmental factors.

Teasdale's (1988) model for depression vulnerability mentioned the likely interaction of biological vulnerability factors with cognitive vulnerability factors, but did not specify how genes might interact with cognitive vulnerability. Beck (1979) focused more on negative early life events playing a role in initial vulnerability, but has since revised his cognitive theory of depression to specifically include a pathway from initial genetic vulnerability to cognitive vulnerability and the expression of depression (Beck, 2008). In addition, recent behavioral genetics data suggest that genetic contributions to depression are likely expressed as a general vulnerability to depression (e.g., cognitive vulnerability) rather than multiple vulnerabilities to individual symptoms of depression (Heun & Hein, 2007).

Thus, identifying specific genetic risk factors for depression and examining their relationship with other vulnerability factors to depression will help construct a more complete model of depression vulnerability. One such genetic risk factor that has been associated with greater risk for depression is a common polymorphism (5-HTTLPR) of the serotonin transporter gene (SLC6A4). Research is now emerging suggesting that the 5-HTTLPR may be associated with cognitive aspects of depression (Beevers & Wells, 2009), but few studies have directly examined this genetic risk factor and cognitive reactivity.

## 1.2 The Serotonin Transporter Gene

### 1.2.1 Overview of Serotonin and the Serotonin Transporter Gene

There is a large amount of evidence that the neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) and its changes and irregularities are associated with emotional states and their dysfunction (Lucki, 1998). Furthermore, abnormalities in 5-HT function, and in particular the serotonin transporter (5-HTT), are found in individuals with mood disorders such as major depression (MDD; Owens & Nemeroff, 1998). Specifically, unmedicated patients with MDD have shown decreased 5-HTT density in the brainstem compared to healthy controls (Malison et al., 1998). In addition, patients with MDD show decreased 5-HTT binding potential in the amygdala and midbrain compared to non-depressed controls (Parsey, Hastings, Oquendo, Huang, Simpson, Arcement, et al., 2006).

Given the research linking 5-HTT with 5-HT and mood disorders, the finding that the 5-HTT is under genetic regulation was of great interest to those studying mood disorders and their etiology, symptoms, and sequellae. The human 5-HTT is encoded by a single gene (SLC6A4) on chromosome 17q11.1-q12 (Lesch, Balling, Gross, Strauss, Wolozin, Murphy, et al., 1994; Lesch, Wolozin, Estler, Murphy, & Riederer, 1993). However, several studies failed to find a common replicated polymorphism in SLC6A4 in patients with mood disorders or in controls (e.g., Lesch, Gross, Franzek, Wolozin, Riederer, & Murphy, 1995). Then, Heils, Lesch, and colleagues discovered a common polymorphism in the transcriptional region upstream of SLC6A4 that they described as the serotonin transporter gene-linked polymorphic region (5-HTTLPR; Heils, Teufel, Petri, Stober, Riederer, Bengel, et al., 1996). They subsequently found that the short (*s*)

variant (characterized by a 44 base pair deletion) of the 5-HTTLPR was associated with decreased 5-HTT expression and 5-HT uptake compared to the long, (*l*) variant (Lesch, Bengel, Heils, Sabol, Greenberg, Petri, et al., 1996). The *s* allele has also been shown to result in decreased 5-HTT binding (Little, McLaughlin, Zhang, Livermore, Dalack, McFinton, et al., 1998) and 5-HTT availability in the dorsal raphe nuclei compared to *ll* homozygotes.

### 1.2.2 Serotonin Transporter Gene and Neuroticism

In addition to differences in 5-HT system, researchers found that *s* allele carriers showed greater levels of neuroticism than *ll* homozygotes (Lesch, Bengel, Heils, Sabol, Greenberg, Petri, et al., 1996). Several meta-analyses of studies conducted over approximately the last 10 years have confirmed the association between higher neuroticism and the *s* allele of 5-HTTLPR (e.g., Sen, Burmeister, & Ghosh, 2004). However, a recent study with over 88,000 subjects failed to find an association between the *s* allele and increased neuroticism (Willis-Owen, Turri, Munafo, Surtees, Wainwright, Brixey, et al., 2005).

### 1.2.3 Serotonin Transporter Gene and Depression

The personality trait of neuroticism has been shown to be a risk factor for developing major depression (e.g., Boyce, Parker, Barnett, Cooney, & Smith, 1991; Hirschfeld, Klerman, Lavori, Keller, Griffith, & Coryell, 1989). In addition, the association between neuroticism and depression has been shown to be due largely to genetic factors (Kendler, Gatz, Gardner, & Pedersen, 2006a). Given the link between neuroticism and depression and the association between the serotonin system and mood disorders, it seems natural to hypothesize that the 5-HTTLPR would be involved in

depression. However, evidence for an association between the *s* allele and depression has been mixed (Lesch, 2003).

While there is a lack of consistent evidence for a direct association between the *s* allele of the 5-HTTLPR and depression, there are several lines of evidence that suggest that stress may moderate the effects of the gene on behavior. An example of this gene-by-environment (G x E) interaction was found in rhesus monkeys, which have a length variation of the 5-HTTLPR that is analogous to humans. Monkeys with the short allele raised in a stressful environment demonstrated greater emotional distress to an examination compared to the *ll* homozygotes raised in the same conditions while there were no differences between allele groups raised in a less stressful environment (Champoux, Bennett, Shannon, Higley, Lesch, & Suomi, 2002). Bennett and colleagues found the same pattern of results examining the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) of rhesus monkeys (Bennett, Lesch, Heils, Long, Lorenz, Shoaf, et al., 2002). Specifically, monkeys with the short allele reared in a stressful environment showed lower concentrations of 5-HIAA in CSF (indicating decreased serotonergic functioning) compared to ll monkeys reared in the same environment, again with no differences between allele groups in the low stress environment. These studies demonstrate an interaction between 5-HTTLPR genotype and stress that leads to changes in serotonin functioning and emotional behavior in monkeys.

The idea that 5-HTTLPR might exert its effect on depression and depressive symptoms only under stressful conditions led to an influential study by Caspi and colleagues that demonstrated a G x E interaction where individuals with the *s* allele were

more likely to develop MDD than *ll* homozygotes only after experiencing several negative life events (Caspi, Sugden, Moffitt, Taylor, Craig, Harrington, et al., 2003). There were no differences between genotype groups when participants had experienced few or no negative life events, but at 4 or more negative life events, *ss* individuals were about twice as likely to have developed MDD compared to *ll* individuals.

This interaction between 5-HTTLPR genotype and stress has since been replicated by other researchers. For example, a large study of twins found same the G x E interaction with *s* allele-carriers at greater risk for developing depression than *ll* homozygotes in the context of life stress (Kendler, Kuhn, Vittum, Prescott, & Riley, 2005). They also found that, specifically, low- to moderate-level stressors (e.g., receiving a negative evaluation at work) rather than major life events (e.g., losing one's job) interact with the 5-HTTLPR and result in increased risk of MDD for *s*-carriers.

Eley and colleagues replicated the G x E effect for 5-HTTLPR and stress on depression among adolescents, although their finding was significant only among females (Eley, Sugden, Corsico, Gregory, Sham, McGuffin, et al., 2004). The effect was also replicated among maltreated children with *ss* homozygote children at a higher risk of developing depression compared to maltreated children with an *l* allele (Kaufman, Yang, Douglas-Palumberi, Houshyar, Lipschitz, Krystal, et al., 2004). This effect was also recently replicated among a sample of elderly Koreans where subjects with an *s* allele exhibited a greater prevalence of depression than *ll* homozygotes after experiencing a number of negative life events (Kim, Stewart, Kim, Yang, Shin, Kim, et al., 2007).

In line with Caspi et al., Wilhelm and colleagues conducted a longitudinal study and found that the 5-HTTLPR interacted with life stress to predict first onset of

depression (Wilhelm, Mitchell, Niven, Finch, Wedgwood, Scimone, et al., 2006). Another longitudinal design by Cervilla and colleagues found increased risk of depression and risk conferred by stressful life events among *ss* homozygotes compared to *l* allele carriers (Cervilla, Molina, Rivera, Torres-Gonzalez, Bellon, Moreno, et al., 2007). Specifically, they found that *ss* homozygotes required exposure to only one stressful life event to achieve the same risk for depression that l carriers achieved after exposure to multiple stressful life events. In addition, a large family-based analysis revealed an association between the 5-HTTLPR and depression with suggestions of an interaction effect with stress (Dick, Plunkett, Hamlin, Nurnberger, Kuperman, Schuckit, et al., 2007).

A few studies have failed to replicate the effects of Caspi and colleagues (e.g., Gillespie, Whitfield, Williams, Heath, & Martin, 2005; Surtees, Wainwright, Willis-Owen, Luben, Day, & Flint, 2006). In addition, two recent meta-analyses have called veracity of the 5-HTTLPR by stress interaction into question (Munafo, Durrant, Lewis, & Flint, 2009; Risch, Herrell, Lehner, Liang, Eaves, Hoh, et al., 2009). However, the conclusions of these meta-analyses have been challenged (Kaufman, Gelernter, Kaffman, Caspi, & Moffitt, 2010; Uher & McGuffin, 2010). In addition, there is a growing body of evidence linking 5-HTTLPR variability with stress response and environmental sensitivity (Caspi, Hariri, Holmes, Uher, & Moffitt, in press). In summary, evidence suggests that the 5-HTTLPR impacts stress response and vulnerability to depression (Caspi et al., in press; Uher & McGuffin, 2010).

Despite the growing evidence of a link between the 5-HTTLPR, stress, and depression vulnerability, a number of questions remain unanswered by this literature. For example, it is unclear by what specific mechanism the 5-HTTLPR interacts with life

stress to increase risk for depression. Also, how might the vulnerability conferred by the 5-HTTLPR relate to cognitive vulnerability to depression, if at all? The relationship between 5-HTTLPR genotype and neural functioning is beginning to provide potential mechanisms by which the polymorphism exerts its effects and these findings lead to potential connections with cognitive vulnerability.

### 1.2.4 Serotonin Transporter Gene and Neural Functioning

Research has recently begun to investigate the neural underpinnings of the association between the 5-HTTLPR and depression. Abnormalities in the morphology and/or functioning of the prefrontal cortex and limbic structures such as the amygdala and anterior cingulate cortex (ACC) are consistent findings in depression (Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Drevets, 2001), therefore, it is perhaps unsurprising that researchers began by exploring the function of these areas and their association with the 5-HTTLPR. Hariri and colleagues were the first to demonstrate that *s* allele carriers exhibit a greater amygdala activation (as measured by fMRI BOLD response) in response to fearful and angry faces compared to *ll* homozygotes (Hariri, Mattay, Tessitore, Kolachana, Fera, Goldman, et al., 2002). This amygdala hyperresponsiveness indicates an intensified neural response to emotional information among *s* allele carriers, which would be consistent with the G x E model discussed above. The effect of the *s* allele on amygdala activation has been replicated in several studies (Bertolino, Arciero, Rubino, Latorre, De Candia, Mazzola, et al., 2005; Hariri, Drabant, Munoz, Kolachana, Mattay, Egan, et al., 2005).

Heinz and colleagues replicated this finding as well, but also found increased coupling between the amygdala and the ventromedial prefrontal cortex (vmPFC) in *s*

allele carriers (Heinz, Braus, Smolka, Wrase, Puls, Hermann, et al., 2005). That is, there was a stronger association between activation to angry and fearful stimuli in the amygdala and the vmPFC in s carriers than in *ll* homozygotes. This is consistent with the idea that frotocortical-amygdala functional connectivity irregularities may underlie the dysfunction observed in the frontal lobes and the amygdala in major depression (Irwin, Anderle, Abercrombie, Schaefer, Kalin, & Davidson, 2004).

Another study found that, among subjects without current or past psychiatric disorders, *s* allele carriers exhibited reduced grey matter volume in both the amygdala and parts of the ACC compared to *ll* homozygotes and, interestingly, the reduced volume of the amygdala was not correlated with increased amygdala activation to angry and fearful stimuli, suggesting that the functional differences are not driven by this structural difference (Pezawas, Meyer-Lindenberg, Drabant, Verchinski, Munoz, Kolachana, et al., 2005). In this same study, they also found that s carriers demonstrated a decreased functional coupling between the amygdala and the ACC compared to *ll* homozygotes. Rao and colleagues used arterial spin labeled perfusion fMRI to detect differences in resting activation of the amygdala and vmPFC. They found that *ss* homozygotes exhibited greater resting amygdala activation and reduced vmPFC resting activation compared to *ll* homozygotes (Rao, Gillihan, Wang, Korczykowski, Sankoorikal, Kaercher, et al., 2007).

These studies have elucidated the relationship between the 5-HTTLPR and the structure and function of certain brain regions. However, none had addressed the interaction between stress, the 5-HTTLPR, and these areas until Canli and colleagues demonstrated that self-reported life stress differentially affected neural activation of *s*

carriers and *ll* homozygotes (Canli, Qiu, Omura, Congdon, Haas, Amin, et al., 2006). Specifically, greater life stress resulted in increased resting amygdala and hippocampus activation for *s* allele carriers and decreased activation for *ll* homozygotes.

In summary, this research on neural functioning and the 5-HTTLPR reviewed above indicates that, compared to *ll* homozygotes, the *s*-allele is associated with greater activation of the amygdala both at rest and when participants were exposed to emotional stimuli. There are also differences between 5-HTTLPR genotype and brain structure and in functional PFC-amygdala connectivity. All of these findings point to differences between 5-HTTLPR genotype and structure and function of brain areas associated with processing and regulation of emotion, but they do not specify how these differences manifest themselves behaviorally or cognitively.

### 1.2.5 Serotonin Transporter Gene and Cognitive Vulnerability to Depression

As reviewed above, most studies found either structural or functional differences in the amygdala between 5-HTTLPR genotype. The amygdala is involved in processing emotional stimuli (Wang, McCarthy, Song, & LaBar, 2005), but interestingly is also involved in directing attention to emotionally relevant information (Davis & Whalen, 2001). This may provide one way in which the neural differences found between 5-HTTLPR genotype are expressed – in attention toward emotionally relevant information. This would also provide a potential link between the 5-HTTLPR and cognitive vulnerability to depression. One potential pathway leading from 5-HTTLPR genotype and greater risk for depression would involve stressful life events leading to a dysphoric mood. Then, once in a dysphoric mood, vulnerable individuals (*s* allele-carriers) would be more likely to attend to emotionally relevant (i.e., dysphoric) information resulting in

greater likelihood of increased duration and intensity of negative mood. This would be consistent with Teasdale's (1988) Differential Activation Hypothesis and the interaction between a biological vulnerability factor and cognitive factors activated by a negative mood.

However, relatively few studies have examined the relationship between 5-HTTLPR genotype and cognitive factors specific to depression vulnerability. Sheikh and colleagues found that the *s* allele and the single nucleotide polymorphism (SNP) of the *l* allele that is functionally equivalent to the *s* allele were associated with increased negative attributional style (Sheikh, Hayden, Singh, Dougherty, Olino, Durbin, et al., 2008). In addition, Beevers, Gibb, McGeary, and Miller (2007) examined the relationship between 5-HTTLPR genotype and biased attention for emotional stimuli in a sample of psychiatric inpatients. They administered a computer-based dot-probe task with anxious-neutral, dysphoric-neutral, and neutral-neutral word pairs to a heterogeneous group of psychiatric inpatients. They found that patients with the *s* allele showed a greater attentional bias for anxious word stimuli than did *ll* homozygotes; however, they found no differences between allele groups for dysphoric word stimuli.

These studies provided initial evidence of a potential association between 5-HTTLPR genotype and cognitive factors associated with depression, but there were also a number of limitations such as small sample size and using a heterogeneous psychiatric inpatient sample. In two studies designed to address these limitations, Beevers, Wells, Ellis, and McGeary (2009) assessed attentional bias with a modified spatial cuing task in a carefully selected sample of community and student volunteers without current or past psychopathology. They found that *s*-carriers in both community and student populations

demonstrated increased difficulty disengaging from dysphoric and happy stimuli compared to *ll* homozygotes. In addition, in the student sample, *s*-carriers demonstrated increased difficulty disengaging from sad, happy, and fear stimuli compared to *ll* participants. There were no differences in engagement of any stimuli for the genotype groups. Overall, this suggests that *s* allele carriers have difficulty disengaging from emotional stimuli, which is consistent with research indicating difficulty regulating cognitive processes and regulating emotion.

These four studies suggest differences in attributional style and attentional bias for emotional information between 5-HTTLPR genotype, but they did not involve a mood manipulation. To test the relationship between 5-HTTLPR genotype and cognitive reactivity, one would need to examine how (or if) these biases change when participants are in a dysphoric mood. Teasdale's (1988) Differential Activation Hypothesis predicts that, among those at risk for depression, cognitive vulnerability factors should be (more) active when an individual is in a dysphoric mood. Therefore, we might expect *s* allele-carriers to demonstrate greater attention for sad stimuli in the context of a negative mood.

Only two studies to date have examined the relationship between 5-HTTLPR genotype and cognitive reactivity. Beevers, Scott, McGeary, and McGeary (2009) examined the relationship between negative automatic thoughts and 5-HTTLPR genotype in healthy college students. Students were administered a film clip to induce either a negative or neutral mood. After the mood induction, participants completed a questionnaire to assess negative automatic thoughts. They found that *ss* homozygotes demonstrated more negative thinking after a negative mood induction than did *ll*

homozygotes while there were no differences in negative thinking after the neutral mood induction.

Hayden, Dougherty, Maloney, Olino, Sheikh, Durbin and colleagues (2008) examined cognitive reactivity in a self-referent encoding task among a sample of 7-year-old children. The children watched a film clip to induce a sad mood and were then asked whether several positive and negative adjectives described them. Afterward, they were given a surprise recall task. Hayden et al. found that *ss* homozygous children endorsed and correctly recalled more negative words following the negative mood induction than did *l* allele carriers.

These two studies provide initial evidence for a connection between 5-HTTLPR genotype and cognitive reactivity, but they also have a number of limitations. In addition to small sample sizes, cognitive measures were assessed only after mood induction rather than before and after the mood induction. In the Hayden et al. (2008) study, this limited the researchers' ability to determine whether this was true cognitive reactivity or whether the results observed in the *ss* children would have been observed in a neutral mood and thus represents a stable factor. The Beevers, Scott, et al. (2009) study compared a negative mood induction to a neutral mood induction and differences were found only in the negative mood condition. Therefore, the greater negative thinking observed in the *ss* participants cannot represent a stable factor. However, it still does not test cognitive reactivity – that is, *change* from pre- to post-mood induction – in a strict sense.

### 1.3 Overview of Research

Early research examining cognitive vulnerability to depression failed to observe evidence of underlying cognitive vulnerabilities in individuals at risk for depression (i.e.,

individuals who had experienced a previous episode of depression); however, as would be indicated by Teasdale's (1988) Differential Activation Hypothesis, these vulnerabilities were observed in at risk individuals when those individuals were currently experiencing a negative mood. This increase in cognitive vulnerability factors after a stressor or negative mood is known as cognitive reactivity and has been associated with risk for depression. In addition, there is now significant evidence that cognitive reactivity is a risk factor for relapse into depression for those who have previously experienced a depressive episode (Lau, Segal, & Williams, 2004). Furthermore, cognitive reactivity in information processing has been associated with risk for increases in depressive symptoms among those who have never experienced a depressive episode (Beevers & Carver, 2003).

A more recently identified risk factor for depression is possession of the short allele of the serotonin transporter gene (5-HTTLPR). In addition, variation in 5-HTTLPR genotype is associated with differences in activation of brain areas associated with processing and regulating emotion and directing attention for emotional information. This led some researchers to speculate that 5-HTTLPR genotype may be associated with cognitive vulnerability factors for depression. The few studies that have examined the association have generally found that short allele-carriers show increased negative cognitive biases.

The research examining the link between 5-HTTLPR status and cognitive vulnerability is promising, but more research is needed to establish the relationship between these two important risk factors for depression (Beevers & Wells, 2008). This

led me to develop a pilot study examining the relationship between 5-HTTLPR genotype and cognitive reactivity in a healthy young adult sample.

# Chapter 2: Pilot Study

## 2.1 Rationale, Aims, and Hypotheses

As reviewed above, there is a significant body of research supporting cognitive vulnerability models of depression. In addition, cognitive vulnerability factors are most easily observed in a negative mood state. As such, cognitive reactivity has been identified as a significant risk factor for both increases in depressive symptoms for individuals without a history of depression and a relapse into depression for individuals with a history of depression. The 5-HTTLPR is also a known risk factor for depression that is active in the context of life stress. Furthermore, the 5-HTTLPR is associated function and connectivity of brain areas implicated in emotional processing and has been associated with cognitive risk factors for depression.

The pilot study was designed to better assess the association between the 5-HTTLPR and cognitive reactivity. In line with studies by Hayden et al. (2008) and Beevers, Scott, et al. (2009), I hypothesized that the *s* allele would be associated with greater cognitive reactivity following a negative mood induction. Specifically, I hypothesized that *ss* individuals would show greater increases in negative thinking and bias for sad faces following the negative mood induction.

## 2.2 Participants

Participants were 156 young adults with low levels of depression symptoms who completed the study as part of a research requirement for an introduction to psychology course. Participants completed the short form of the Beck Depression Inventory (BDI; Beck & Steer, 1993) during mass pretesting. Participants whose scores were below a 4 on the short form of the BDI were contacted about participating in the current study. Of the

183 participants who attended the laboratory session, 10 were eliminated for having a BDI-II score greater than 9 and did not complete the study tasks. A further 9 participants were eliminated for endorsing a past depressive episode on the IDD-L (Zimmerman, Coryell, Corenthal, & Wilson, 1986) and 8 were eliminated for currently taking medication for a psychiatric disorder.

## 2.3 Self-Report Measures

**2.3.1 Demographics.** Participants provided their age, gender, ethnicity, level of education, socioeconomic status, current and past medication use, and family history of psychological/psychiatric problems.

**2.3.2 Depression Symptoms.** The Beck Depression Inventory II (BDI-II; Beck, Steer, & Brown, 1996) is a 21-item self-report questionnaire that assesses symptoms of depression. See section 4.4.2 (page 41) below for more detailed information on the BDI-II.

**2.3.3 Depression History.** The Inventory to Diagnose Depression – Lifetime Version (IDD-L; Zimmerman, Coryell, Corenthal, & Wilson, 1986) is a 22-item self-report inventory designed to assess the presence and severity of the diagnostic criteria for a major depressive episode. The IDD-L has good convergent validity for symptom severity and good agreement with a diagnostic interview (Goldston, O'Hara, & Schartz, 1990).

**2.3.4 Rumination.** The Response Styles Questionnaire (RSQ; Nolen-Hoeksema & Morrow, 1991) measures how an individual responds to a negative mood. The RSQ has more recently been revised to remove item overlap and now contains two 5-item subscales: brooding and reflecting (Treynor, Gonzalez, & Nolen-Hoeksema, 2003). The

new version of the RSQ has shown adequate reliability and validity (Treynor et al., 2003).

**2.3.5 Recent Psychopathology.** The Symptom Checklist – 90- Revised (SCL-90-R; Derogatis, 1994) is a 90-item measure that measures overall psychopathological symptom severity with a global symptom index (GSI) and is most often divided into subscales of somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid ideation, and psychoticism. The SCL-90-R has shown adequate good internal consistency, concurrent validity, and discriminant validity (Schmitz, Hartkamp, Kiuse, Franke, Reister, & Tress, 2000).

**2.3.6 Dysfunctional Attitudes.** The Dysfunctional Attitudes Scale (DAS; Weissman, 1979) was originally a 100-item scale that is most often divided into two 40-item forms (A & B). The DAS-A is used more frequently and has since been refined into two equivalent 9-item short forms (DAS-SF1 & DAS-SF2; Beevers, Strong, Meyer, Pilkonis, & Miller, 2007). Both short forms were highly correlated with the DAS-A (>.9) and have demonstrated good reliability, convergent validity, and predictive validity (Beevers, Strong, Meyer, Pilkonis, & Miller, 2007).

**2.3.7 Current Mood.** The Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1992) contains 65 adjectives describing feelings on 6 scales: depression-dejection, anger-hostility, anxiety-tension, fatigue, vigor, and confusion. We created a short form of the POMS using 12 descriptors (4 each from the depression, anger, and anxiety scales). The items with the best factor loadings for each of the three scales were used. Internal consistency for the POMS in the pilot study was good ($\alpha$ = .86).

Participants also indicated current mood on a single item scale (SIS) that ranged from 1 (very sad) to 9 (very happy).

## 2.4 Genotyping

Participants provided a saliva sample to genotype for the 5-HTTLPR polymorphism of the serotonin transporter gene. For more information, please see the "Genotyping" section 4.6 (page 45) below.

## 2.5 Dot-Probe Task

### 2.5.1 Dot-Probe Materials

Facial photo stimuli expressing sadness, happiness, and fear were selected from the Pictures of Facial Affect (POFA) photo set developed by Ekman and Friesen (1976). A set of 12 faces were selected from each emotion category for a total of 36 emotion stimuli. Each emotion face was then paired with a face of the same actor depicting a neutral expression. Faces were used rather than word stimuli due to the success of other recent studies in detecting a bias using these types of visual stimuli (e.g., Gotlib, Krasnoperova, Yue, & Joormann, 2004; Joormann & Gotlib, 2007).

### 2.5.2 Dot-Probe Procedure

The set of 36 image pairs was presented in 3 blocks in each dot-probe session for a total of 108 trials per session. Each trial consisted of a white fixation cross on a black background in the middle of the screen for 1000 ms, followed by an image pair for 1000 ms. Following the offset of the images, a small single white asterisk probe on a black background appeared in the location of one of the images and remained on the screen until the participant pressed a corresponding key on the keyboard to indicate the location of the probe. The computer recorded the latency and accuracy of each response. Each

type of stimulus (emotional or neutral) appeared on each side of the screen with equal probability. Similarly, the probe appeared on the left or right with equal probability.

### 2.5.3 Dot-Probe Presentation

Please see 4.7.3 (page 48) below for a more detailed description of task presentation. Briefly, participants will be told that their goal is to determine the location of the asterisk probe as quickly and accurately as possible. They will use their left index finger to press the "D" key when the asterisk appears on the left and will use their right index finger to press the "K" key when the asterisk appears on the right. Participants will complete 10 practice trials using neutral-neutral pairs. If participants fail to respond accurately to at least 9 of the 10 practice trials, they will be asked to repeat the practice until they achieve this level of accuracy.

## 2.6 Procedure

Participants who scored less than 4 on the short-form of the Beck Depression Inventory (BDI-SF) during mass pre-testing were invited to participate in this study (*N*=218). Upon arrival to the laboratory, depression severity was re-assessed using the BDI-II. Those with scores greater than 9 were thanked, debriefed, and given full credit for the study. Participants who qualified (*N*=173) completed additional questionnaires including demographics, the IDD-L, SCL-90-R, RSQ, DAS short form, a short form of the POMS, and the SIS. After data collection, participants were excluded if they reported currently taking medication for an emotional problem and if they qualified for a past episode of MDD on the IDD-L. This resulted in a sample size of 156 participants.

After completing questionnaires, participants completed a dot-probe task (described below) to assess attentional bias for emotional information. They then

underwent a sad mood induction procedure (MIP). During the MIP, participants listened to Samuel Barber's *Adagio for Strings* while thinking of a time in their life when they were very sad. The prompt to think of a sad time in their life remained on the screen for the duration of the song (approximately 7 minutes). After the mood induction, participants filled out an alternate form of the DAS short form, POMS short form, and SIS and then completed the dot-probe task again. Participants also provided a saliva sample for genetic analyses.

## 2.7 Pilot Study Results

### 2.7.1 Participant Characteristics

Genetic analyses indicated that of the 156 participants, 45 possessed two long alleles (*ll*), 77 had one short and one long allele (*sl*), and 34 were short allele homozygotes (*ss*). Participant characteristics for each genotype group as well as the sample as a whole are shown in Table 1. One way ANOVAs revealed no significant differences between genotype groups on age $F(2, 153) = 2.62$, $p = ns$ or BDI-II score $F(2, 153) < 1$, $p = ns$. There were also no group differences in number of women $\chi^2(2, N = 156) = 4.79$, $p = ns$ or number of participants identifying as Hispanic or Latino $\chi^2(2, N = 156) = 2.48$, $p = ns$. In addition, there were no significant differences between genotype groups on baseline questionnaires including all subscales of the SCL-90-R, the RSQ subscales, baseline DAS scores, and baseline mood measured by the POMS subscales, all $F$s$(2, 153) < 2.8$, $p$s $= ns$.

Table 1

*Pilot Study Demographic Characteristics*

| | 5-HTTLPR Status | | |
|---|---|---|---|
| Demographic | *ll* | *sl* | *ss* |
| *n* | 45 | 77 | 34 |
| Age (Years) | 19.4 (1.5) | 18.9 (1.0) | 18.8 (1.0) |
| Depressive symptoms (BDI-II) | 3.2 (2.3) | 2.9 (2.8) | 3.0 (2.9) |
| General Psychopathology (SCL-90-R) | 0.3 (0.2) | 0.3 (0.3) | 0.2 (0.2) |
| Rumination (RSQ) | 8.7 (4.7) | 9.3 (5.3) | 9.5 (5.8) |
| Baseline Dysfunctional Attitudes (DAS-SF) | 17.5 (3.4) | 17.1 (4.1) | 17.4 (4.1) |
| Baseline Sad Mood (POMS) | 0.2 (0.5) | 0.4 (0.8) | 0.3 (0.9) |
| Baseline Anxious Mood (POMS) | 1.2 (1.6) | 1.3 (1.6) | 1.1 (1.6) |
| Baseline Angry Mood (POMS) | 0.6 (1.1) | 0.9 (2.1) | 0.5 (0.9) |

*Note. BDI-II = Beck Depression Inventory – II; SCL-90-R = Symptom Checklist-90-Revised; RSQ = Response Style Questionnaire; DAS-SF = Dysfunctional Attitudes Questionnaire-Short Form; POMS = Profile of Mood States*

### 2.7.2 Data Reduction

We analyzed response latencies on the dot-probe only from correct responses. Eliminating incorrect responses resulted in a loss of 0.7% of data. In addition, to minimize the influence of outliers, we eliminated response latencies for each participant that were faster than 150 ms or slower than 1000 ms. This resulted in a further loss of 0.9% of the data.

### 2.7.3 Manipulation Check

A one sample t-test indicated that change scores on both the SIS $t(155) = -14.94$, $p < .001$, and the POMS depression subscale $t(153) = 10.8$, $p < .001$ from pre- to post-mood induction were significantly different from zero, suggesting that the mood induction was generally successful in manipulating mood. A 3 (genotype group: *ll*, *sl*, *ss*) x 2 (time: pre-mood induction, post-mood induction) repeated measures ANOVA revealed no significant interaction between genotype group and mood response on the SIS or between genotype group and mood response on the POMS depression subscale, $Fs(2, 153) < 1$, $ps = ns$. This indicates that the genotype groups did not differ in their mood response to the negative mood induction.

### 2.7.4 Cognitive Reactivity of Attention Bias

Consistent with the procedure of Gotlib et al. (2004), attentional bias scores were calculated for each participant for each of the four training sessions using the following equation (cf. Mogg, Bradley, & Williams, 1995):

Attentional bias score = ½[(RpLe – RpRe) + (LpRe – LpLe)] (1)

where R = right position, L = left position, p = probe, and e = emotional stimulus. Therefore, RpLe indicates the mean response latency when the probe is in the right position and the emotional stimulus is in the left position, and so on.

A 3 (genotype group: *ll*, *sl*, *ss*) x 2 (time: pre-mood induction, post-mood induction) repeated measures ANOVA revealed a significant interaction between genotype group and attention bias for happy faces, $F(2, 153) = 4.09$, $p = .019$, $\eta^2 = .05$. Post hoc paired t-tests revealed that this effect was driven by a significant increase in attention bias for happy faces (+13.2 ms) among the *ll* genotype group, $t(44) = -3.1$, $p =$

.004. The *sl* group demonstrated a non-significant increase (+4 ms) in bias for happy faces, $t(76) = -1.66$, $p = ns$, while the *ss* group demonstrated a non-significant decrease (-5.7 ms) in bias for happy faces, $t(33) = 1.4$, $p = ns$. Additionally, a linear polynomial contrast indicated a linear relationship between number of *s* alleles and bias score for happy faces $F(2, 153) = 8.18$, $p = .005$. (See Figure 1 below; this section, page 33).

A 3 (genotype group: *ll*, *sl*, *ss*) x 2 (time: pre-mood induction, post-mood induction) repeated measures ANOVA revealed no significant interaction between genotype group and attention bias for sad faces, $F(2, 153) < 1$, $p = ns$. Due to the exploratory nature of this study, further exploratory analyses and planned comparisons were conducted despite the non-significant interaction. Though there was not a significant interaction, visual inspection of the data indicated that the changes were in the expected direction. In addition, a linear polynomial contrast indicated a near trend-level linear relationship between number of *s* alleles and bias score for sad faces $F(2, 153) = 2.47$, $p = .12$. (See Figure 1 below; this section, page 33). Further exploratory analyses indicated that the standard errors of the mean for sad stimuli were approximately three times greater than standard errors of the mean for happy stimuli. This indicates greater variability in responding for the sad stimuli compared to the happy stimuli.

A 3 (genotype group: *ll*, *sl*, *ss*) x 2 (time: pre-mood induction, post-mood induction) repeated measures ANOVA revealed no significant interaction between genotype group and attention bias for fear faces, $F(2, 153) < 1$, $p = ns$. Visual inspection of the data indicated minimal change for all genotype groups and a linear polynomial contrast indicated no linear relationship between number of *s* alleles and bias score for fear faces $F(2, 153) < 1$, $p = ns$. (See Figure 1 below; this section, page 32).

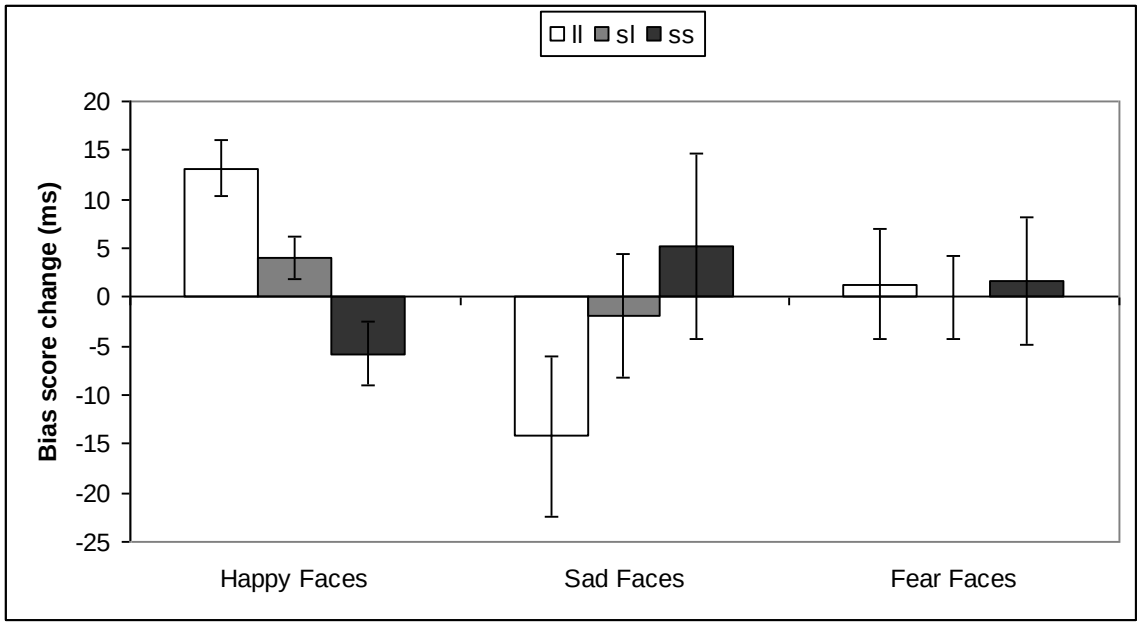


*Figure 1.* Bias change for 5-HTTLPR genotype from pre- to post-mood induction for each stimulus type. Error bars represent standard error of the mean.

### 2.7.5 Cognitive Reactivity of Dysfunctional Attitudes

A 3 (genotype group: *ll*, *sl*, *ss*) x 2 (time: pre-mood induction, post-mood induction) repeated measures ANOVA revealed no significant interaction between genotype group and DAS-SF scores, $F(2, 146) < 1$, $p = ns$. However, there was a main effect for time, $F(1, 146) = 5.03$, $p = .026$, with all genotype groups demonstrating an increase in dysfunctional attitudes after the mood induction. Again, due to the exploratory nature of this study, further exploratory analyses and planned comparisons were conducted despite the non-significant interaction. Exploratory post-hoc analyses indicated that the *ll* group experienced a non-significant increase (+0.4) in DAS-SF score from pre- to post-mood induction, $t(38) < 1$, $p = ns$. The *sl* group demonstrated a trend level significant increase (+0.6) in DAS-SF score from pre- to post-mood induction, $t(75) = -1.66$, $p = .1$. The *ss* group experienced a non-significant increase (+0.9) in DAS-SF score from pre- to post-mood induction, $t(33) = 1.34$, $p = ns$. Though the interaction was

not significant, a visual inspection of the data indicates the expected pattern of results with *ss* participants experiencing the greatest increase in negative thinking and *ll* participants experiencing the smallest increase, though this linear effect is not statistically significant, $F(2, 153) < 1$, $p$ = *ns*. (See Figure 2 below).

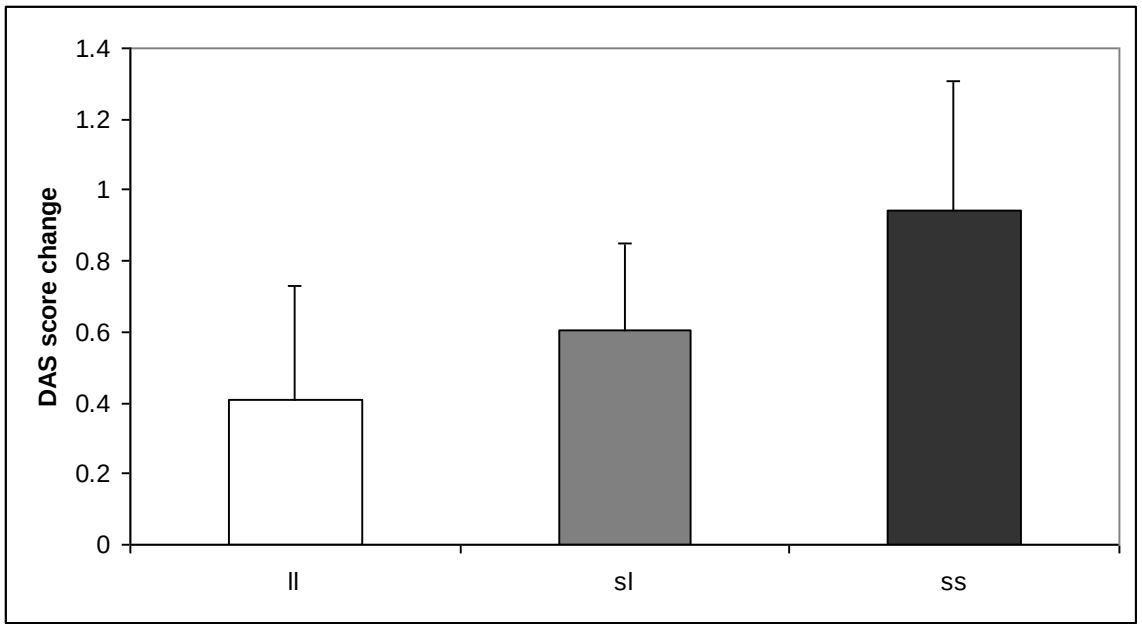


*Figure 2*. DAS-SF score change for 5-HTTLPR genotype groups from pre- to post-mood induction. Error bars represent standard error of the mean.

### 2.8 Pilot Study Summary and Limitations

My hypothesis that *ss* individuals would show greater increases in negative thinking and bias for sad faces following the negative mood induction was partially supported. Though the effects were not statistically significant, the direction of the effects was in the expected direction. In addition, there was an unexpected effect indicating that 5-HTTLPR genotype influenced cognitive reactivity for happy faces following the mood induction. Specifically, attention bias for happy faces increased among the *ll* group after a negative mood induction, while the *sl* and *ss* groups did not

change significantly. Also, the apparent linear effect for number of *s* alleles and strength of attention bias is consistent with previous research (see Beevers, Wells, Ellis, & McGeary, 2009).

This study is one of the first to demonstrate that 5-HTTLPR genotype status affects cognitive reactivity after a negative mood induction. However, this study has a number of limitations. First, this study used a convenience sample of young adults who were screened for present and past psychopathology with self-report questionnaires rather than a clinical interview. While the use of the questionnaires reduces the likelihood that the results of the study were due to the presence of current or past psychopathology, a clinical interview would be a more thorough assessment method. Second, the study design does not eliminate the possibility that the results are due to a priming or repetition effect. All participants performed the dot-probe task twice: once before the mood induction and once after, a separation of only 7 to 8 minutes. Due to the lack of a control group that did not receive a mood induction, it is possible that the results were due to priming by the first dot-probe rather than due to the mood manipulation. Third, the stimuli for each of the emotion categories (happy, sad, or fear) were presented 36 times in each dot-probe task. This resulted in 18 trials for each emotion category where the probe followed the emotional stimulus and 18 trials where the probe followed the neutral stimulus. This low number of trials may not have resulted in stable attention bias scores and the resulting variability may have obscured otherwise present effects. As mentioned above, this may have been particularly true for sad stimuli; they demonstrated standard errors of the mean approximately 3 times greater than those for happy faces. Increasing the number of trials on the dot-probe task will be important for establishing a stable

attention bias score for each emotion category. Additionally, often initial behavioral genetics findings are often not replicated in subsequent studies (Ioannidis, Ntzani, Trikalinos, & Contopoulos-Ioannidis, 2001). Therefore, replication of the pilot study results is important to ensure the validity of the findings.

# Chapter 3: Current study

## 3.1 Rationale

As reviewed above, there is growing interest in the relationship between the 5-HTTLPR and cognitive risk factors for depression. Though in its beginning stages, research linking the 5-HTTLPR and cognitive aspects of depression is accumulating. The pilot study described above demonstrated a relationship between the 5-HTTLPR and cognitive reactivity to a negative mood induction, but there were a number of limitations to be addressed. The current study was designed to replicate the finding of the pilot study and to improve upon the pilot study's methodology.

## 3.2 Improvements on the Pilot Study

### 3.2.1. Improvement 1

Participants were more carefully screened for current and past psychopathology with a clinical interview. This helped ensure that effects of current or past psychopathology were not responsible for any effects observed in the study.

### 3.2.2 Improvement 2

Participants completed the study over the span of two sessions separated by at least 24 hours to help reduce any priming or recency effects. In one session, participants underwent a neutral mood induction and completed the DAS and dot-probe task. In another session participants completed a negative mood induction, an alternate form of the DAS, and dot-probe task. In addition, the order of these sessions was counterbalanced. (See Figure 4 below; section 3.2.9, page 44). This counterbalancing ensured that any priming or previous exposure effects were distributed across both the neutral and negative mood induction sessions.

### 3.2.3 Improvement 3

The fear faces category was eliminated from the dot-probe task in order to increase the number of trials for the sad and happy faces while maintaining a reasonable task length. Though this resulted in a loss of the ability to test for specificity of an observed attention bias, it allowed more reliable measurement of the critical happy and sad biases. The current study presented emotional-neutral face pairs from each emotion category (happy or sad) 56 times for a total of 112 trials. This resulted in 28 trials where the probe followed the happy stimulus and 28 trials where the probe followed the sad stimulus. This represents a 55% increase in emotion-probe trials, which was designed to increase bias score reliability. These numbers of trials are consistent with studies that have found significant effects with the dot-probe task, which typically administer 24 or more trials per stimulus type (e.g., Gotlib, Krasnoperova, Yue, & Joormann, 2004; Joormann, Talbot, & Gotlib, 2007). See the method section below for more details on the dot-probe task.

### 3.2.4 Improvement 4

The procedure for administering the DAS in the current study was made more consistent with the procedure used by Segal and colleagues (1999; 2006). Specifically, the two, full 40-item forms of the DAS were administered rather than the 9-item short forms. This was designed to reduce the possibility that lack of effects for dysfunctional attitudes would be due to measurement issues. In addition, consistent with Van der Does (2002b), the music for the mood induction continued to play while the participant filled out questionnaires.

### 3.2.5 Improvement 5

The word "imagine" replaced the word "think" in the instructions for the mood induction (e.g., "Imagine a time in your life when you were very sad.") to help improve the potency of the mood induction procedures. Previous research has shown that mental imagery is more effective in eliciting emotions than similar verbal representations (Holmes & Mathews, 2010).

To obtain more objective data about the content of the imagery during the mood induction, participants wrote narrative accounts of their mood induction imagery. At the end of each experimental session, participants typed the details of the content of their imagery during the mood induction. These narratives were rated for both level of detail and level of sadness by independent raters blind to the mood induction condition (i.e., sad vs. neutral).

### 3.2.6 Improvement 6

A number of lines of research suggest that serotonin and the serotonin system affect memory processes (Buhot, Martin, & Segu, 2000; Meneses, 1999). In rats, the *s* allele of the 5-HTTLPR is associated with poorer memory performance (Olivier, Jans, Blokland, Broers, Homberg, Ellenbroek, et al., 2009). It is also associated with poorer memory in an elderly human sample (O'Hara, Schroder, Mahadevan, Schatzberg, Lindley, Fox, et al., 2007). The *ss* genotype has also been associated with poorer memory than the *ll* genotype after an acute tryptophan depletion (ATD) procedure; however, outside the context of the ATD, the *ss* group actually demonstrated better memory than the *ll* group (Roiser, Muller, Clark, & Sahakian, 2007). Another study using an ATD procedure and emotional word stimuli found that the *ss* group

demonstrated poorer recall of positive words after the ADT (Firk & Markus, 2009). There were no differences between genotype for negative words after the ATD or for either stimulus category before the ATD. As such, there is some evidence that the 5-HTTLPR may impact memory functioning, but only one study to date has examined the relationship between 5-HTTLPR and emotional stimuli. Therefore, a task assessing memory for the emotional faces presented in the dot probe task was added.

## 3.3 Hypotheses

### 3.3.1 Hypothesis I

Consistent with the pilot study, it was predicted that the *ll* group would show a significant increase in attention bias for happy faces following the negative mood induction compared to the neutral mood induction.

### 3.3.2 Hypothesis II

The pilot study did not reveal a statistically significant association between 5-HTTLPR genotype and cognitive reactivity for attention bias for sad faces, but the effects were in the expected direction. Improvements in the design of the current study were designed to reduce variability and improve the stability of the attention bias score. Therefore, I predicted that the effect will be similar in direction to the effect observed in the pilot study. Namely, that the *ss* group would demonstrate an increase in bias for sad faces following the negative mood induction compared to the neutral mood induction.

### 3.3.3 Hypothesis III

The pilot study did not reveal a statistically significant association between 5-HTTLPR genotype and cognitive reactivity for dysfunctional attitudes, but the effects

were in the expected direction. Using the 40-item DAS measures was expected to reduce any potential measurement errors due to using the DAS short form in the pilot study. I hypothesized that the effects would be similar to the direction observed in the pilot study. Specifically, I predicted that the *ss* genotype group would show greater increases in dysfunctional attitudes compared to the *sl* and *ll* groups.

# Chapter 4: Research Design and Methods

## 4.1 Study Participants

Study participants were 180 young adults recruited through the Introductory Psychology (PSY 301) subject pool at the University of Texas at Austin. Interviewers used structured clinical interviews to determine presence and history of psychopathology. In addition, all participants completed the Beck Depression Inventory – II (BDI-II; Beck, Steer, & Brown, 1996) Participants partially fulfilled a research requirement by completing this study.

## 4.2 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were:

Inclusion Criteria

a. Score of 4 or lower on the BDI Short Form during mass pretesting of the PSY 301 subject pool indicating low levels of depressive symptoms.
b. Fluent in written and spoken English. This is necessary due to the fact that the principal investigator and research assistants are not fluent in other languages and most of the instruments have not been translated or validated in other languages.
c. 18 years of age or older.
d. Participating in the PSY 301 subject pool.

Exclusion Criteria

a. Score of 13 or higher on the BDI-II indicating significant depressive symptoms at the time of the study.

b. Lifetime history of any Axis I disorder as assessed by the SCID *except for the following*: specific phobia, alcohol abuse remitted at least 1 month.

c. Currently taking psychotropic medication. This is due to the fact that psychotropic medication may impact information processing (Merens, Van der Does, & Spinhoven, 2007), and many psychotropic medications have direct or indirect effects on the serotonin system.

**4.3 Diagnostic Assessment**

To assess exclusion criteria, the patient version of the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1995) was administered on the first day of study participation. Five assessors participated in more than 40 hours of training, wherein they practiced interviewing skills, learned diagnostic criteria for DSM-IV (American Psychiatric Association, 1994), role-played interviews, and rated 10 hours of recorded interviews. To minimize rater drift, weekly meetings were conducted with all assessors where one SCID audio recording was reviewed and discussed. Furthermore, twenty percent of all interviews were rated by an independent assessor. Agreement between study and independent assessor was perfect for diagnoses for mood, anxiety, psychotic, and eating disorders. Agreement for substance dependence ($\kappa = .66$) and alcohol abuse ($\kappa = .79$) was acceptable.

**4.4 Self-Report Measures** (Appendix A).

**4.4.1 Demographics.** Participants provided their age, gender, ethnicity, level of education, socioeconomic status, current and past medication use, and family history of psychological/psychiatric problems.

**4.4.2 Depression Symptoms.** The Beck Depression Inventory II (BDI-II; Beck, Steer, & Brown, 1996) is a 21-item self-report questionnaire that assesses symptoms of depression. The BDI-II is one of the most widely used self-report measures of depressive symptomology and has demonstrated adequate internal consistency, test-retest reliability and construct validity (Beck, Steer, & Garbin, 1988; Dozois, Dobson, & Ahnberg, 1998). Scores range from 0 to 63 with scores of 0 to 12 representing nondepressed (Dozois, Dobson, & Ahnberg, 1998).

**4.4.3 Anxiety Symptoms.** The Inventory of Depression and Anxiety Symptoms (IDAS; Watson, O'Hara, Simms, Kotov, Chmielewski, McDade-Montez, et al., 2007) is a 64-item scale that measures symptoms of depression and anxiety. The scales demonstrate good internal consistency as well as convergent and discriminant validity (Watson et al., 2007). The 99-item expanded version was administered, which includes the following anxiety subscales: social anxiety, panic, traumatic intrusions, and anxious mood.

**4.4.4 Dysfunctional Attitudes.** The Dysfunctional Attitudes Scale (DAS; Weissman, 1979) was originally a 100-item scale that is most often divided into two 40-item forms (A & B). The two forms have been shown to have good internal consistency and are highly correlated with each other (Weissman & Beck, 1978).

**4.4.5 Most Depressed Episode Severity.** The Patient Health Questionnaire – 9 (PHQ-9) consists of the first nine questions of the Patient Health Questionnaire (Spitzer, Kroenke, Williams, & The Patient Health Questionnaire Primary Care Study Group, 1999). It is a self-report measure which assesses the symptoms of Criterion A for a major depressive episode using DSM-IV criteria. These symptoms include: depressed mood,

anhedonia, appetite change, sleep disturbance, psychomotor agitation or retardation, loss of energy, feelings of worthlessness or guilt, diminished concentration and suicidal thoughts or attempts. Participants are asked to respond using a 4-point continuum. The original version has been modified to assess for a past episode of depression and has been shown to be valid and reliable in demonstrating a past clinical depressive episode (Cannon, Tiffany, Coon, Scholand, McMahon, & Leppert, 2007). The sum of the nine PHQ items was used as an indicator of the severity of participants' most depressed episode.

**4.4.6 Current Mood.** A brief (8-item) affective adjective list (AAL) for measuring current sad and happy mood was created using words from the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1992) and the Positive and Negative Affect Schedule – Expanded Form (PANAS-X; Watson & Clark, 1994). The sad mood scale was used in the pilot and dissertation studies. The happy mood scale was used only in the current study.

The four descriptors with the highest factor loadings for the depression-dejection scale of the POMS (sad, blue, hopeless, worthless) were used to construct the sad mood scale. Internal consistency for this scale was good in the pilot study ($\alpha$ = .86) and acceptable in the current study ($\alpha$ = .67). Three adjectives from the PANAS-X positive affect scale (happy, cheerful, joyful) plus one additional adjective (pleasant) were used to construct the happy mood scale. This scale had good internal consistency ($\alpha$ = .89).

Participants also completed 2 single-item scales (SIS) of current sad and happy mood that range from 1 (not at all sad) to 9 (very sad) and 1 (not at all happy) to 9 (very

happy). The sad and happy SIS were significantly associated with the sad and happy affective adjective lists, r = .41, $p < .001$ and r = .69, $p < .001$, respectively.

## 4.5 Mood Inductions

### 4.5.1 Sad Mood Induction

During the sad mood induction, participants listened to Samuel Barber's *Adagio for Strings* while imagining a time in their life when they were very sad. This type of mood induction procedure (MIP) has been shown to be effective in eliciting a temporary negative mood (Van der Does, 2002b). In the pilot study, 81% of participants responded to this negative mood induction as indicated by at least a one point drop on the sad SIS. In the current study, approximately 94% of participants experienced either a 1 point increase in sad mood or a 1 point decrease in happy mood on the SIS after the sad mood induction.

### 4.5.2 Neutral Mood Induction

During the neutral mood induction[1], participants listened to Wolfgang Amadeus Mozart's *Concerto no. 17 in G Major* while thinking about their day in as much detail as possible. The prompt will ask them to focus on all the things that they have done that day rather than any emotions they might have felt. This piece of music was selected to match the negative MIP music for length of time and style of music (classical instrumental). This neutral MIP appeared to be appropriately neutral with approximately 80% of participants indicating no change in sad or happy mood on the sad and happy SIS.

[1] It is not clear that a neutral mood can be "induced", per se. However, for ease of reading, the neutral music condition is referred to as a neutral mood induction.

### 4.5.3 Mood Induction Narratives

To help increase the potency of the mood inductions and to provide data on the content of the autobiographical events recalled during the inductions, participants typed a description of what they imagined during the mood inductions. Before each mood induction, participants were instructed that they should imagine the events (either a sad time in their life or the details of their day) in as much detail as possible and that they would be writing about the events at the end of that session. At the end of each session (Day 1 and Day 2), participants typed their narrative and this data was saved on the computer.

Five independent assessors, blind to the mood induction condition, rated each narrative on its level of detail (0-4, 0 = none or very minimal, 4 = very detailed), degree of sadness (0-4, 0 = not sad at all, 4 = very sad), and coded for the type of event(s) described. The internal consistency among the 5 raters was good for level of sadness (Chronbach $\alpha = .87$) and detail ($\alpha = .89$) in the sad mood induction narratives. Internal consistency for level of sadness in the neutral induction narratives could not be computed because of a lack of variance (i.e. almost all ratings were coded as 0). Internal consistency for level of detail in the neutral induction narratives was excellent ($\alpha = .93$). Internal consistency for the type of event described in the sad MIP condition was also excellent ($\alpha = .97$). The mean percent of narratives coded as each event type can be seen in Figure 3 below.

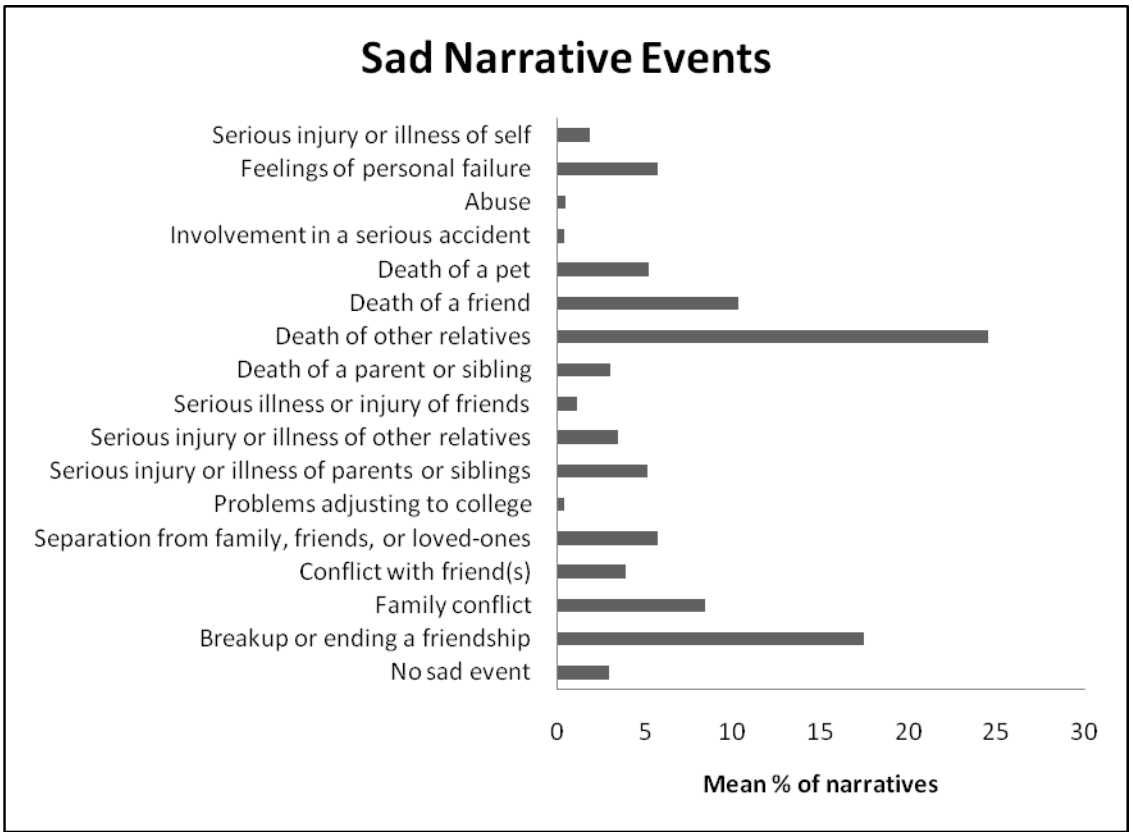


*Figure 3.* Mean percentage of sad narratives rated as each event type.

### 4.6 Genotyping

Genomic DNA was isolated from buccal cells using a modification of published methods (Freeman, Powell, Ball, Hill, Graig, & Plomin, 1997; Lench, Stanier, & Williamson, 1988; Meulenbelt, Droog, Trommelen, Boomsma, & Slagboom, 1995; Spitz, Moutier, Reed, Busnel, Marchaland, Roubertoux, et al., 1996). The cheeks and gums are rubbed for 20 s with three sterile, cotton-tipped wooden swabs. The swabs are placed in a 50-ml capped polypropylene tube containing lysis buffer (500 µl of 1 *M* Tris-HCl; 200 mM disodium ethylene diaminetetracetic acid (EDTA), pH 8.0; 500 µl of 10% sodium docecyl sulfate; and 100 µl of 5 *M* sodium chloride). The subjects then rinse out the

mouth vigorously with 10 ml of distilled water for 20 sec and this was added to the 50-ml tube. The tubes were stored at 4°C until the DNA was extracted.

The 5HTTLPR gene, which maps to 17q11.1-17q12, contains a 43 bp insertion/deletion in the 5' regulatory region of the gene (Heils et al., 1996). The VNTR in the promoter appears to be associated with variations in transcriptional activity: the long variant (528 bp) has approximately three times the basal activity of the shorter promoter (484 bp) with the deletion (Lesch et al., 1996). The assay is a modification of the method of Lesch and colleagues (Lesch et al., 1996). The primer sequences are: forward, 5'- GGCGTTGCCGCTCTGAATGC-3' (fluorescently labeled), and reverse, 5'-GAGGGACTGAGCTGGACAACCAC-3'. These primer sequences yield products of 484 or 528 bp. Allele sizes were be scored by two investigators independently and inconsistencies were reviewed and rerun when necessary.

## 4.7 Dot-Probe Task

### 4.7.1 Dot-Probe Materials

As in the pilot study, facial photo stimuli expressing sadness and happiness were selected from the Pictures of Facial Affect (POFA) photo set developed by Ekman and Friesen (1976). A set of 8 faces were selected from each emotion category (happy and sad) and then paired with a face of the same actor depicting a neutral expression for a total of 16 face pairs.

### 4.7.2 Dot-Probe Procedure

The set of 16 face pairs were presented in 7 blocks in each dot-probe session for a total of 112 trials per session. As in the pilot study, each trial consisted of a white fixation cross on a black background in the middle of the screen for 1000 ms, followed

by an image pair for 1000 ms. Longer stimulus durations (compared to those used in anxiety research) have been more successful in eliciting biases in depression and have been suggested to allow participants time for more elaborative processing (Mogg & Bradley, 2005). Following the offset of the images, a small single white asterisk probe on a black background appeared in the location of one of the images and remained on the screen until the participant pressed a corresponding key on the keyboard to indicate the location of the probe. The computer recorded the latency and accuracy of each response. Each type of stimulus (emotional or neutral) appeared on each side of the screen with equal probability. Similarly, the probe appeared on the left or right with equal probability. See Figure 3 below for a visual representation of the task sequence.

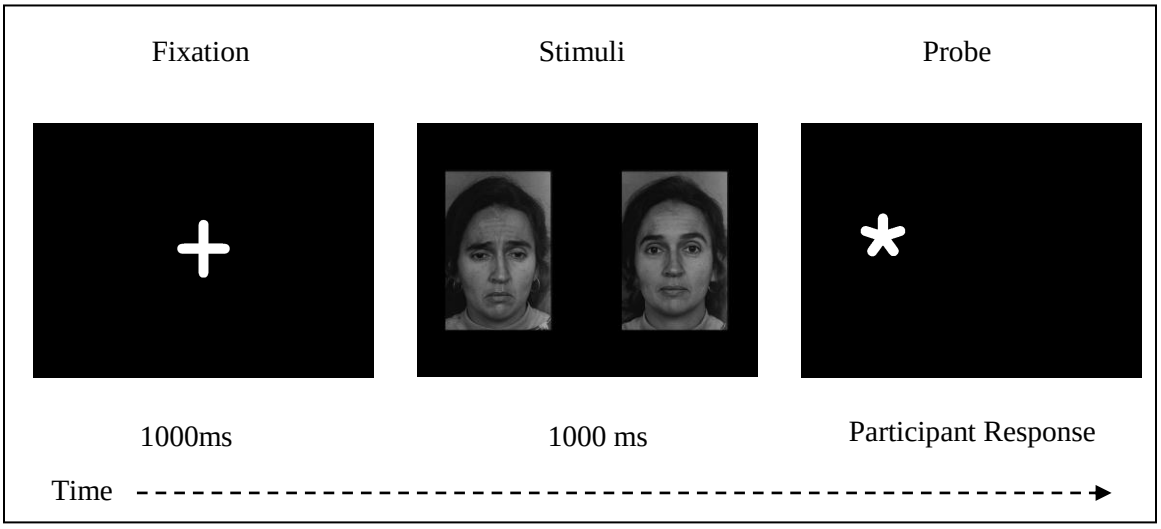


*Figure 4.* Dot-probe task sequence. Note: fixation and probe are not to scale.

### 4.7.3 Dot-Probe Presentation

The task was presented on an IBM-compatible computer and a Dell 20-inch color monitor. E-Prime software controlled stimulus duration and was used to record response

latency and accuracy. The size of each POFA image was approximately 12.7 x 19 cm when presented on the screen. The pictures in each pair were approximately 21 cm apart when measured from each center and were presented in the left and right halves of the screen. Participants sat approximately 58 cm from the screen. Participants were told that their goal was to determine the location of the asterisk as quickly and accurately as possible. They used their left index finger to press the "D" key when the asterisk appeared on the left and used their right index finger to press the "K" key when the asterisk appeared on the right. Participants completed 10 practice trials using neutral-neutral pairs. If participants failed to respond accurately to at least 9 of the 10 practice trials, they were asked to repeat the practice until they achieved this level of accuracy.

#### 4.7.4 Dot-Probe Data Analysis

Consistent with previous research (Gotlib et al., 2004), attentional bias scores were calculated for each participant using the following equation:

$$\text{Attentional bias score} = \tfrac{1}{2}[(\text{RpLe} - \text{RpLe}) + (\text{LpRe} - \text{LpLe})] \quad (1)$$

where R = right position, L = left position, p = probe, and e = emotional word stimulus. Therefore, RpLe indicates the mean response latency when the probe is in the right position and the emotional word stimulus is in the left position, and so on. Positive bias scores indicate a bias toward the emotional stimuli while negative bias scores indicate a bias away from the emotional stimuli.

### 4.8 Memory Task

#### 4.8.1 Memory Task Procedure

After completing the dot-probe task on Day 2, participants completed a filler task for approximately 12 minutes and then performed an incidental recognition task where

they viewed individual faces one at a time and were queried whether they had seen that actor displaying that particular facial expression in the dot-probe task. Ten faces (5 each from happy and sad conditions) from the dot probe task were presented during the memory task. In addition, 10 previously unseen faces displaying happy or sad emotional expressions were presented. In addition to the 24 faces presented during the dot probe task, 24 previously unseen expressions by those same actors were presented for a total of 48 trials. All emotional valences were equally represented across seen and unseen stimuli and were balanced across actor gender. Participants responded to the images by pressing the "K" key on the keyboard if they thought they had seen that actor with that expression during the eye tracking task and by pressing the "D" key if they had not seen that face. The order of the presentation of the faces was randomized for each participant and the size of the images was identical to the dot-probe task (12.7 x 19 cm).

#### 4.8.2 Memory Task Data Analysis

Memory for emotional faces was calculated based on signal detection theory. Signal detection threshold (d') is a measure of the ability to differentiate target stimuli from distracter stimuli. It was calculated for each emotion by subtracting the z-score transformed false alarms (i.e., indicating "yes" to previously unseen stimuli) for a particular emotion from the z-score transformed hits (i.e., indicating "yes" to previously presented stimuli) for that emotion. Higher scores indicate better ability to distinguish targets from distracters.

I also measured a memory response bias for each emotion category. Response bias was calculated by subtracting the number of false negative responses (i.e., indicating "no" to previously presented stimuli) for a given emotion from the number of false

alarms for that emotion and then dividing the difference by the sum of false negatives and false alarms. Positive scores indicate a more liberal response style (a "yes-saying" bias) while negative scores indicate a more conservative style (a "no-saying" bias).

**4.9 Procedure**

As mentioned above, participants in the PSY 301 subject pool who scored 4 or lower on the BDI short form during mass pretesting were be invited to the laboratory to participate in the study. Upon arrival in the laboratory, participants were assessed with the SCID and, as mentioned above, participants with past or current major psychopathology were excluded. Participants scoring 13 or above on the BDI-II and participants currently taking psychotropic medication were also excluded.

Qualifying participants were then be randomized into one of two conditions, which were identical except for the order in which participants completed the mood inductions. In condition A, participants completed the self-report questionnaire battery followed by the SCID interview. They then completed the sad mood induction followed by the DAS, current mood measures, and the dot-probe task. Next, they typed a narrative describing the sad event they had imagined in the sad MIP. Participants also provided a saliva sample for genetic analysis, which concluded their participation on day 1. Participants then returned to the laboratory 24 to 96 hours later for day 2 of the study and completed a neutral mood induction. The neutral MIP was followed by the alternate form of the DAS, the current mood measures, and dot-probe task again. They then completed a filler task using word stimuli that lasted for approximately 12 minutes. Next, they completed the memory task and wrote a narrative describing the details of their day as they imagined it during the neutral MIP.

Consistent with Van der Does (2002b), the music from both mood inductions continued to play as the participants completed the DAS. Condition B was identical to condition A except that participants in condition B completed the neutral mood induction on day 1 and the negative mood induction on day 2. See Figure 5 below for an outline of the procedure.

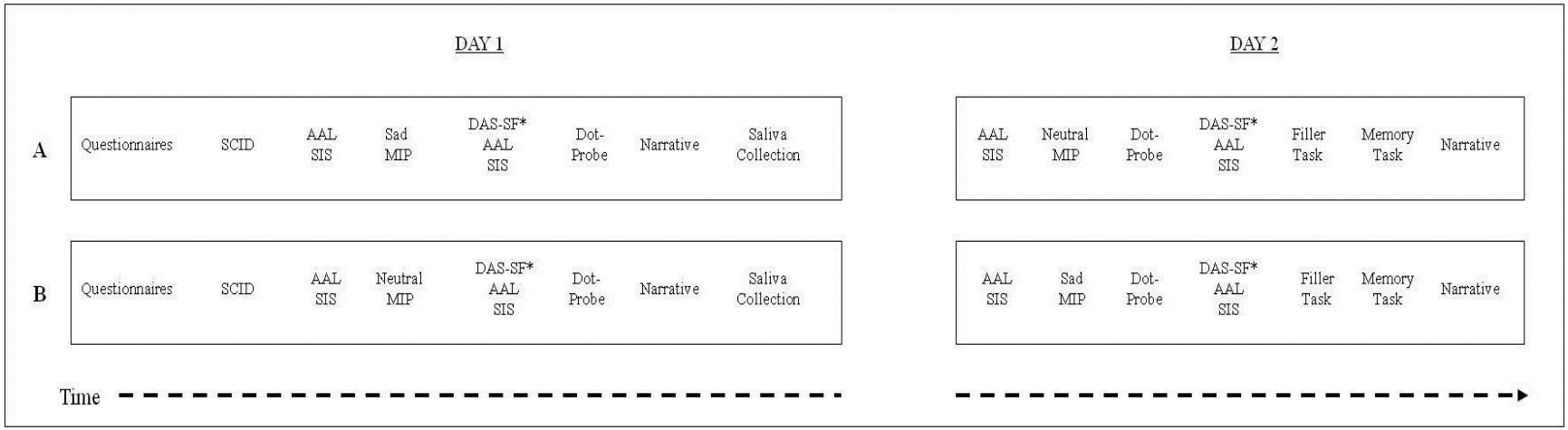


*Figure 5.* Dissertation study procedure. * The order of the two equivalent forms of the DAS was counterbalanced across participants and across conditions (A or B); the music from the mood induction continued to play while participants completed the DAS. SCID = Structured Clinical Interview for DSM-IV. AAL = Affective Adjective List. SIS = single item scales for positive and negative mood. MIP = mood induction procedure. DAS= dysfunctional attitudes scale.

# Chapter 5: Results

## 5.1. Sample Characteristics

Descriptive statistics for the sample are presented in Table 2 by 5-HTTLPR status. There were no significant differences between allele groups for age, $F(2, 178) < 1$, $p = .99$, depressive symptoms, $F(2, 179) < 1$, $p = .97$, social anxiety symptoms, $F(2, 179) < 1$, $p = .81$, panic symptoms, $F(2, 179) = 1.24$, $p = .29$, PTSD symptoms, $F(2, 179) = 1.88$, $p = .16$, general anxiety symptoms, $F(2, 179) < 1$, $p = .66$, most depressed episode severity, $F(2, 166) < 1$, $p = .85$, or gender, $\chi^2(2, 178) = 3.71$, $p = .16$. In addition, there was not a significant difference in allele distribution by race, $\chi^2(6, 176) = 1.61$, $p = .45$. Due to the extremely low number of Native American participants ($n = 1$), analysis of allele distribution by race was also calculated excluding this participant with very similar results, $\chi^2(5, 175) = 1.42$, $p = .49$. The lack of significant differences in allele distribution across races reduces the threat of population stratification, but does not eliminate it entirely. The most conservative approach would be to analyze data from only Caucasian participants (Hutchison, Stallings, McGeary, & Bryan, 2004), and such an approach is routinely used in behavior genetics studies (e.g., Alexander, Kuepper, Schmitz, Osinsky, Kozyra, & Hennig, 2009; Wray, James, Gordon, Dumenil, Ryan, Coventry, et al., 2009; Zalsman, Huang, Oquendo, Burke, Hu, Brent, et al., 2006). To balance the strength of utilizing the full sample (i.e. statistical power) with the strength of limiting the sample to Caucasians (i.e. reduction in potential sampling bias), primary analyses were calculated for both the full sample and for the Caucasian-only sample.

Table 2

*Current study Demographic Characteristics*

| | 5-HTTLPR Status | | |
|---|---|---|---|
| Demographic | *ll* | *sl* | *ss* |
| *n* | 51 | 89 | 40 |
| Age (Years) | 18.8 (1.0) | 18.8 (2.0) | 18.8 (0.7) |
| Gender (Female/Male) | 63%/37% | 46%/54% | 55%/45% |
| Race (*n*) | | | |
| Native American | 0 | 1 | 0 |
| Asian | 2 | 15 | 11 |
| Black/African American | 5 | 5 | 1 |
| White/Caucasian | 34 | 53 | 16 |
| "Multiple" | 3 | 3 | 4 |
| "None of the above" | 6 | 11 | 6 |
| Did not report | 1 | 1 | 2 |
| Depressive symptoms (BDI-II) | 3.4 (3.1) | 3.5 (3.3) | 3.5 (2.9) |
| Social anxiety symptoms (IDAS) | 7.1 (2.4) | 6.8 (2.1) | 7.0 (2.3) |
| Panic symptoms (IDAS) | 9.3 (2.1) | 9.2 (1.8) | 9.8 (2.2) |
| PTSD symptoms (IDAS) | 4.9 (1.2) | 4.7 (0.9) | 5.1 (1.7) |
| General anxiety symptoms (IDAS) | 12.8 (3.8) | 12.3 (3.5) | 12.3 (3.5) |
| Most depressed episode severity (PHQ) | 6.3 (4.9) | 6.5 (4.7) | 5.9 (4.5) |

*Note. BDI-II = Beck Depression Inventory – II; IDAS = Inventory of Depression and Anxiety Symptoms; PHQ = Patient History Questionnaire*

## 5.2 Manipulation Check

### 5.2.1 Single item scale

The sad mood provocation successfully increased sad mood, $t(179) = 14.59$, $p < .001$, Cohen's $d = 2.18$, and decreased happy mood, $t(179) = 13.81$, $p < .001$, Cohen's $d = 2.06$. Participants experienced a mean increase of 2.6 points ($SD = 2.4$) for sadness and mean decrease of 2.1 points ($SD = 2.1$) for happiness on the respective 9-point scales. The neutral mood provocation did not change sad, $t(179) < 1$, $p = .41$, or happy, $t(179) < 1$, $p = .93$, mood. There were no effects of 5-HTTLPR genotype on change in sad, $F(2, 179) < 1$, $p = .99$, or happy, $F(2, 179) = 1.39$, $p = .25$, mood after the neutral provocation. Similarly, there was no genotype effect for change in happy mood after the sad mood provocation, $F(2, 179) < 1$, $p = .55$. However, there were significant differences between groups in change in sad mood following the sad provocation, $F(2, 179) = 3.59$, $p = .03$, Cohen's $d = .4$, with the *sl* group showing a less pronounced increase in sad mood ($M = 2.2$, $SD = 2.5$) than *ss* group ($M = 3.2$, $SD = 2.4$) and the *ll* group ($M = 2.9$, $SD = 2.1$).

### 5.2.2 Affective Adjective List

The sad mood provocation successfully increased sad mood, $t(176) = 10.6$, $p < .001$, Cohen's $d = 1.6$, and decreased happy mood, $t(176) = 12.54$, $p < .001$, Cohen's $d = 1.89$, as measured by the Affective Adjective List (AAL). Participants experienced a mean increase of 1.5 points ($SD = 1.9$) for sadness and mean decrease of 2.8 points ($SD = 2.9$) for happiness on the respective AAL scales. The neutral mood induction did not change sad mood, $t(176) < 1$, $p = .44$. However, participants did experience a slight ($M$ change = -0.44, $SD = 1.7$), but statistically significant decrease in happy mood after the neutral mood induction, $t(176) = 3.45$, $p < .001$, Cohen's $d = .26$.

There were no effects of 5-HTTLPR genotype on change in sad, $F(2, 176) < 1$, $p = .58$, or happy, $F(2, 176) < 1$, $p = .69$, mood after the sad induction. Similarly, there

was no genotype effect for change in sad, $F(2, 176) = 2.73$, $p = .068$, or happy, $F(2, 176) = 1.5$, $p = .23$, mood after the neutral mood provocation.

### 5.2.3 Narratives

Narratives from sad mood inductions ($M = 2.3$, $SD = 0.85$) were rated as more sad than narratives from neutral mood inductions ($M = 0.002$, $SD = 0.02$), $t(159) = 34.42$, $p < .001$, Cohen's $d = 5.46$. The level of detail in neutral mood narratives ($M = 2.33$, $SD = 1.02$) was slightly, but significantly, greater than the level of detail in sad narratives ($M = 2.11$, $SD = 0.92$), $t(159) = 2.86$, $p = .005$, Cohen's $d = .45$.

Furthermore, the rating of sadness and level of detail in the sad narratives were positively correlated, $r = .46$, $p < .001$. The average sadness rating for the sad narrative was also correlated with change in happy, $r = -.18$, $p = .023$, and sad, $r = .19$, $p = .013$, mood after the sad mood induction. Average level of detail in sad narratives was correlated with change in happy mood, $r = -.23$, $p = .003$, but not sad mood, $r = .09$, $p = .25$.

Mean level of sadness of narratives did not differ between genetic groups for sad, $F(2, 159) = 2.47$, $p = .09$, or neutral, $F(2, 163) < 1$, $p = .59$, narratives. Similarly, level of detail did not differ between genetic groups for sad, $F(2, 163) = 1.86$, $p = .16$, or neutral, $F(2, 159) = 2.37$, $p = .1$, narratives.

## 5.3 Dysfuctional Attitudes

### 5.3.1. Influential Cases and Distributional Assumptions

Cook's distance values were calculated for DAS scores from both neutral and sad mood inductions. Data points with a Cook's distance of greater than 1 are often considered to have a disproportionately large influence. No participants had a Cooks distance value greater than 1 for DAS after neutral mood induction or sad mood induction; therefore all data points were retained for the analyses.

Distributional assumptions were assessed with the Shapiro-Wilk Test of Normality. Both DAS after neutral mood induction, Shapiro-Wilk (180) = .99, $p$ = .27, and DAS after sad mood induction, Shapiro-Wilk (180) = .98, $p$ = .1, were not significantly different from a normal distribution.

### 5.3.2 Primary Data Analyses

A 3 (5-HTTLPR genotype: *ss*, *sl*, *ll*) x 2 (mood induction: neutral, sad) repeated measures analysis of variance (ANOVA) was conducted with change in dysfunctional attitudes total score from neutral to sad mood as the within subjects factor. There were no significant main effects for 5-HTTLPR genotype, $F(2, 177) < 1$, $p$ = .89, or mood induction, $F(1, 177) = 3.36$, $p$ = .07, on dysfunctional attitudes. Similarly, the interaction between genotype and mood induction was not significant, $F(2, 177) = 1.97$, $p$ = .14. Entering change in sad mood after the sad mood induction as a covariate did not substantially change the analyses.

The Caucasian group analysis was very similar to the analysis conducted collapsing across race. The main effect for genotype, $F(2, 100) < 1$, $p$ = .94, main effect for mood induction, $F(1, 100) = 3.17$, $p$ = .08, and the interaction between the two, $F(2, 100) = 1.47$, $p$ = .24, were all not statistically significant.

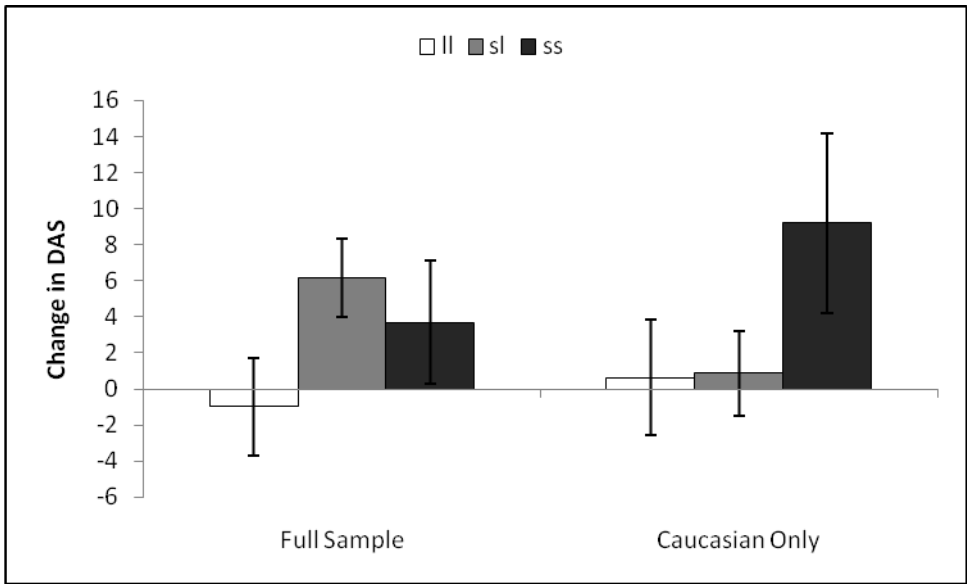


*Figure 6.* DAS score change from neutral mood to sad mood split by 5-HTTLPR genotype groups. Error bars represent standard error of the mean.

I also examined the effects of mood induction order on DAS scores. There were no differences in neutral mood induction DAS scores, $t(179) < 1$, $p = .54$, or sad mood induction DAS scores, $t(179) < 1$, $p = .39$, based on mood induction order. In addition, change in DAS score from neutral mood induction to sad mood induction did not differ based on mood induction order, $F(1, 178) < 1$, $p = .79$.

## 5.4 Attention Bias

### 5.4.1 Data Reduction

We deleted trials with incorrect responses (0.6% of all trials) and did not use them for analyses. Furthermore, we deleted reaction times that were faster than 150 ms or slower than 1000 ms (1.1%). Together, these procedures resulted in the exclusion of less than 1.8% of the data.

### 5.4.2. Influential Cases and Distributional Assumptions

Cook's distance values were calculated for attention bias scores for happy and sad stimuli after both neutral and sad mood inductions. As mentioned above, data points with a Cook's distance of greater than 1 are often considered to have a disproportionately large influence. Two data points were found to have a Cook's distance value greater than 1 for

attention bias for happy faces after the neutral mood induction and were removed from further analyses. One data point was removed from attention bias for happy faces after the sad mood induction and two data points were removed from attention bias for sad faces after the sad mood induction. No participants had a Cooks distance value greater than 1 for attention bias for sad faces after the neutral mood induction. Thus, a total of 4 data points were removed.

Distributional assumptions for attention bias score (ABS) were assessed with the Shapiro-Wilk Test of Normality. Only ABS for happy faces after the neutral mood induction was not significantly different from a normal distribution, Shapiro-Wilk (176) = .992, $p$ = .45. Attention bias score for happy faces after a sad mood induction, Shapiro-Wilk (176) = .95, $p$ < .001, differed from a normal distribution. Similarly, ABS for sad faces after a neutral mood induction, Shapiro-Wilk (176) = .982, $p$ = .02, and after a sad mood induction, Shapiro-Wilk (176) = .976, $p$ = .004, differed from a normal distribution (see Figure 7 below for an example). Upon visual inspection, the distributions that differed from normal closely resembled normal distributions but were somewhat leptokurtic. With this elevated kurtosis, common power transformations of the data (e.g., square, square root, cube, cube root, log) did not help normalize the distributions. Analyses were conducted using assumptions of a normal distribution. Hence, results should be interpreted with some caution.

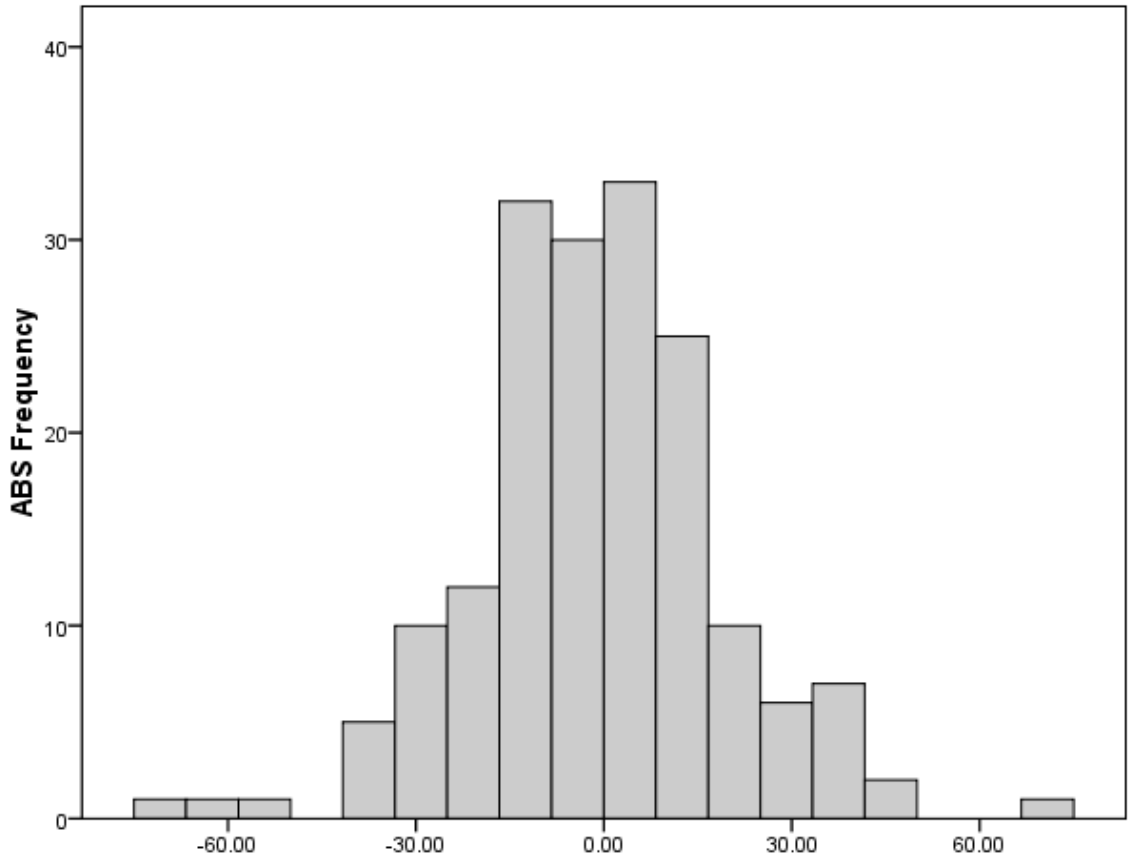


*Figure 7.* Distribution of ABS for sad faces after the neutral mood induction.

### 5.4.3 Preliminary Analyses

**5.4.3.1 Lateral Dominance.** Because participants responded with the right and left hand, differences between hands in reaction time and reaction time standard deviation were analyzed. There were no differences between left and right hand responses in reaction time, $t(179) < 1$, $p = .32$, or reaction time standard deviation, $t(178) = 1.04$, $p = .29$.

**5.4.3.2 Sleep and Sleepiness.** Self-reported hours of sleep the previous night and self-reported sleepiness were significantly and negatively associated, $r = -.25$, $p = .001$. Hours of sleep the previous night was not related to reaction time in the dot-probe task, $r = -.02$, $p = .77$, or reaction time standard deviation, $r = .05$, $p = .56$. Similarly, self-reported sleepiness was not related to reaction time, $r = .06$, $p = .44$ or

reaction time standard deviation, r = .08, $p$ = .29. Hours of sleep, $F(2, 165) < 1$, $p$ = .82, and sleepiness, $F(2, 165) = 1.71$, $p$ = .18, did not differ by genetic group.

**5.4.3.3 Alcohol Consumption.** Self-reported alcohol consumption the night previous to the initial testing session was generally low. A majority of participants (95%) reported consuming zero drinks the previous night. Only one participant reported consuming 3 alcoholic drinks the previous night and no participants reported more than 3 drinks. Number of drinks consumed the previous night was not associated with reaction time, r = -.10, $p$ = .21, or reaction time standard deviation, r = .07, $p$ = .39. Furthermore, previous night alcohol consumption did not differ by genetic group, $F(2, 155) = 1.98$, $p$ = .14.

### 5.4.4 Primary Data Analyses

A 3 (5-HTTLPR genotype: *ss*, *sl*, *ll*) x 2 (mood induction: neutral, sad) x 2 (stimulus valence: happy, sad) mixed plot analysis of variance (ANOVA) was conducted with change in attention bias score from neutral to sad mood as the within subjects factor. There were no significant main effects for 5-HTTLPR genotype, $F(2, 173) < 1$, $p$ = .41, or stimulus valence, $F(1, 173) < 1$, $p$ = .75, on change in bias score. However, there was a significant main effect for mood induction, $F(1, 173) = 3.99$, $p$ = .047, partial $\eta^2$ = .023, on bias score change. This effect was driven by greater attention bias for emotional stimuli after the sad mood induction ($M$ = 2.8 ms) compared to after the neutral mood induction ($M$ = -0.5 ms).

Interactions between genotype and mood induction, $F(2, 173) = 2.09$, $p$ = .13, genotype and stimulus valence, $F(2, 173) = 1.73$, $p$ = .18, mood induction and stimulus valence, $F(1, 173) < 1$, $p$ = .73, as well as the 3-way interaction between genotype, mood induction, and stimulus valence, $F(2, 173) < 1$, $p$ = .45, were not significant. Taking a conservative approach, due to the lack of significant interactions, follow-up analyses were not conducted for the full sample.

Analyses using only Caucasian participants revealed no significant main effects for 5-HTTLPR genotype, $F(2, 97) < 1$, $p = .38$, stimulus valence, $F(1, 97) = 1.68$, $p = .19$, or mood induction, $F(1, 97) = 1.37$, $p = .24$, on change in attention bias. Similarly, interactions between genotype and stimulus valence, $F(2, 97) = 2.19$, $p = .12$, mood induction and stimulus valence, $F(1, 97) = 1.08$, $p = .3$, as well as the 3-way interaction between genotype, mood induction, and stimulus valence, $F(2, 97) < 1$, $p = .79$, were not significant. However, the interaction between genotype and mood induction was significant, $F(2, 97) = 4.4$, $p = .015$, partial $\eta^2 = .083$. This was driven by a significant increase in bias ($M = 9.6$ ms, $SD = 13.0$) for emotional stimuli in the *ss* genotype group after the sad mood induction compared to the neutral mood induction, $t(14) = 2.78$, $p = .015$, Cohen's $d = .77$. The *sl* group demonstrated a non-significant increase ($M = 3.1$ ms, $SD = 18.1$) in attention bias for emotional stimuli, $t(52) = 1.23$, $p = .22$, Cohen's $d = .18$, and the *ll* group showed a non-significant decrease ($M = -5.6$ ms, $SD = 18.2$) in bias for emotional stimuli, $t(31) = 1.73$, $p = .09$, Cohen's $d = .39$. Furthermore, there was a significant difference between genotype groups for attention to emotional stimuli after the neutral mood induction, $F(2, 99) = 3.26$, $p = .043$, Cohen's $d = .32$, but not after the sad mood induction, $F(2, 98) = 1.21$, $p = .3$. See Figure 8.

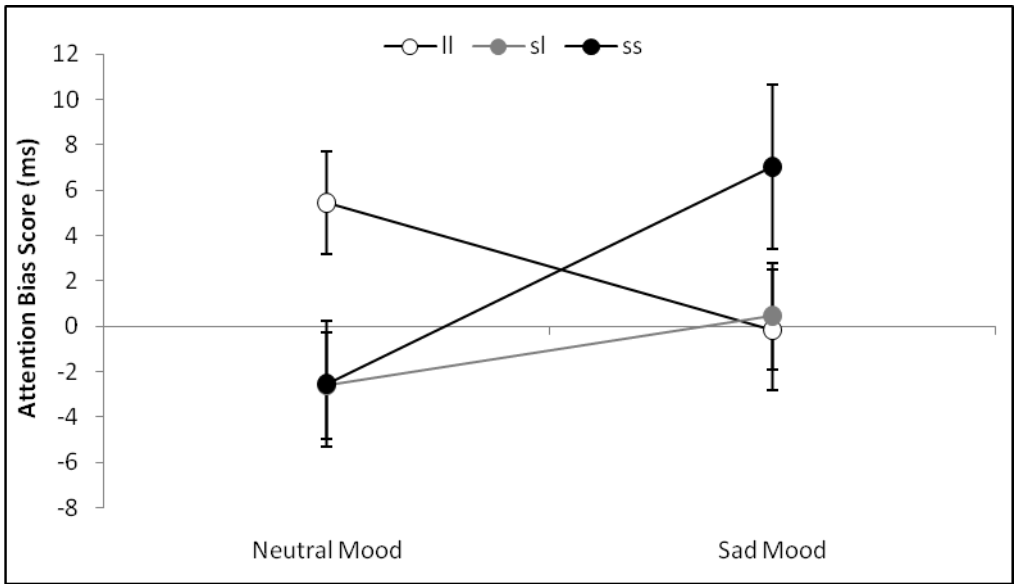


*Figure 8.* Attention bias scores in the Caucasian sample for emotional faces during the neutral and sad mood inductions by genotype group. Error bars represent the standard error of the mean.

In addition, a linear polynomial contrast indicated a significant linear relationship between number of *s* alleles and change in bias score from the neutral MIP condition to the sad MIP condition, $F(2, 97) = 4.4$, $p = .015$. That is, there was a greater increase in bias for emotional faces with each short allele. See Figure 9.

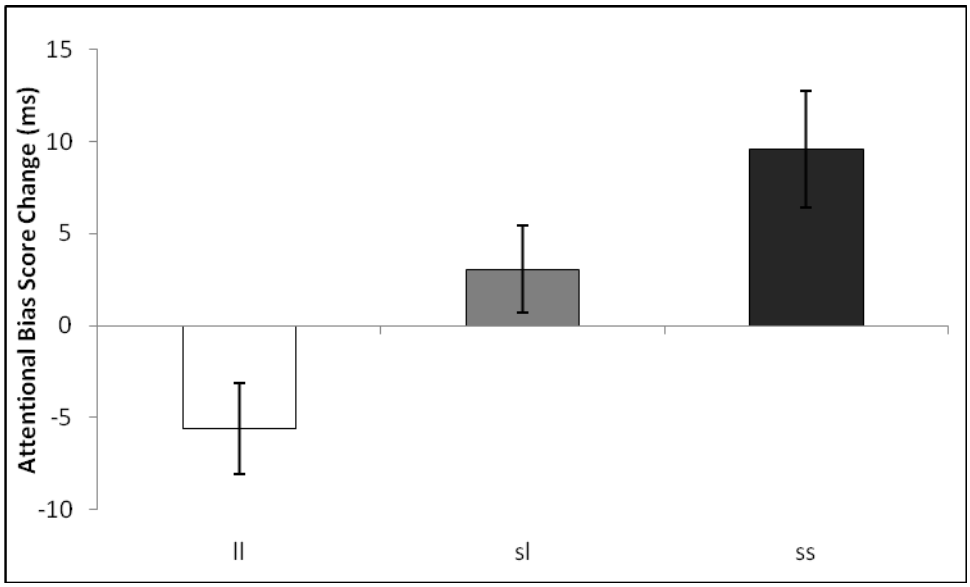


*Figure 9.* Attention bias scores change in the Caucasian sample for emotional faces by genotype group. Error bars represent the standard error of the mean.

I also examined the effects of mood induction order on attention bias scores. There were no differences in attention bias for happy stimuli after the neutral mood

induction, $t(176) < 1$, $p = .96$, or for happy stimuli after the sad mood induction, $t(177) = 1.02$, $p = .31$, based on mood induction order. Similarly, there were no differences in bias for sad stimuli after the neutral, $t(178) = 1.68$, $p = .95$, or sad, $t(176) < 1$, $p = .87$, mood inductions based on mood induction order. In addition, change in attention bias score from neutral mood induction to sad mood induction did not differ based on mood induction order for happy, $F(1, 175) < 1$, $p = .41$, or sad, $F(1, 176) < 1$, $p = .33$, stimuli.

**5.5 Memory for Emotional Faces**

One way ANOVAs revealed no differences between 5-HTTLPR genotype groups in memory accuracy (d') for happy, $F(2, 165) < 1$, $p = .48$, or sad, $F(2, 165) = 1.53$, $p = .22$, facial stimuli. Similarly, there were no differences between genotype group for response bias for happy, $F(2, 165) = 1.22$, $p = .29$, or sad, $F(2, 165) < 1$, $p = .91$, stimuli.

Analyses for the Caucasian sample did not differ substantially from the analyses collapsing across race. There were no differences between 5-HTTLPR genotype groups in d' for happy, $F(2, 93) = 1.1$, $p = .34$, or sad, $F(2, 93) < 1$, $p = .49$, facial stimuli. Similarly, there were no differences between genotype group for response bias for happy, $F(2, 93) = 1.95$, $p = .14$, or sad, $F(2, 93) < 1$, $p = .82$, stimuli.

There were no differences between Day 2 mood induction groups (sad or neutral) in memory accuracy for happy or sad stimuli, $F$s < 1, $p$s > .9, or in response bias for happy, $F(1, 165) = 1.96$, $p = .16$, or sad stimuli, $F(1, 165) < 1$, $p = .36$. However, sad mood (as measured by the single-item scale) immediately prior to the memory task was significantly and negatively associated with memory accuracy for happy stimuli, $r = -.16$, $p = .036$. Sad mood was not associated with memory accuracy for sad stimuli, $r = -.06$, $p = .42$. Happy mood was not associated with memory accuracy for happy, $r = .13$, $p = .08$, or sad, $r = .02$, $p = .76$, stimuli. Sad mood showed a marginally significant positive association with response bias for sad stimuli, $r = .15$, $p = .056$, but was not associated

with response bias for happy stimuli, r = .02, *p* = .8. Happy mood was not associated with response bias for sad, r = -.03, *p* = .68, or happy, r = .02, *p* = .76, stimuli.

Attention bias for sad stimuli on the day of the memory task was not associated with memory accuracy or response bias for happy or sad stimuli, all | r| < .12, all *p* > .11. Similarly, attention bias for happy stimuli was not associated with memory accuracy or response bias for happy or sad stimuli, all | r| < .06, all *p* > .5.

**5.6 Results Summary**

A summary of the results of the current study can be found in Table 3 (below, this section, page 68).

Table 3

*Current Study Results Summary*

| Section | Results Summary |
|---|---|
| Sample Characteristics | No significant differences across allele groups for age, gender, race, depressive symptoms, anxiety symptoms, or most depressed episode severity. |
| Manipulation Check | Significant increases in sadness and decreases in happiness after the sad mood induction, *p*s < .001. No changes in sad mood after the neutral mood induction. Slight decrease in happy mood following the neutral mood induction measured by the affective adjective list, $p < .001$, $d = .26$, but not the single item scale. |
| Narratives | Sad narratives were rated as significantly more sad than neutral narratives by blind raters, $p < .001$, $d = 5.46$. Sadness ratings of sad narratives were associated with change in sad and happy mood after the sad mood induction *p*s < .025. |
| Dysfunctional Attitudes | No significant effects of genotype on dysfunctional attitudes. |
| Lateral Dominance | No differences between right and left hand in mean reaction time or reaction time standard deviation in the dot-probe task. |
| Sleep and Sleepiness | Neither hours of sleep nor self-rated sleepiness were associated with mean reaction time or reaction time standard deviation in the dot-probe task. |
| Alcohol Consumption | 95% of participants reported consuming 0 drinks the night previous to Day 1 of the study. Number of drinks was not associated with mean reaction time or reaction time standard deviation in the dot-probe task |
| Attention Bias | Significant main effect of mood induction, $p = .047$, partial $\eta^2 = .023$, in the full sample driven by an increase in bias for emotional faces in the sad mood condition. A significant genotype X mood induction interaction, $p = .015$, partial $\eta^2 = .083$, in the Caucasian sample driven by an increase in bias for emotional faces in the *ss* genotype group after the sad mood induction. A significant linear relationship between number of *s* alleles and increase in bias for emotional faces in the Caucasian sample. |
| Memory for Emotional Faces | Sad mood immediately prior to the memory task was negatively associated with memory for happy stimuli, $r = -.16$, $p = .036$. No significant genetic associations. |

# Chapter 6: Discussion

## 6.1 5-HTTLPR Variation and Cognitive Reactivity

These are the first studies to examine the relationship between the 5-HTTLPR and cognitive reactivity. Previous research has examined the relationship between the 5-HTTLPR and cognitive variables after a sad mood (Beevers, Scott, et al., 2009; Hayden et al., 2008), but these are the first studies to examine cognitive variables in both a euthymic and a sad mood in the same sample.

### 6.1.1 Dysfunctional Attitudes and 5-HTTLPR Variation

The 5-HTTLPR was not significantly associated with change in dysfunctional attitudes after a sad mood induction in the pilot study, but the effects were in the expected direction. That is, there was a visual trend for a greater number of short alleles to be (non-significantly) associated with increased cognitive reactivity of dysfunctional attitudes. Similarly, the current study did not find a significant association between 5-HTTLPR variation and change in dysfunctional attitudes from neutral to sad mood conditions, but, again, the visual trend was for the short allele to be associated with a greater increase in dysfunctional attitudes. Thus, there was no statistically significant support for Hypothesis III, but the effects were in the expected direction.

Previous research has demonstrated increased negative thinking in short allele homozygotes after a sad mood induction in both children (Hayden et al., 2008) and young adults (Beevers, Scott, et al., 2009). The lack of a significant genetic effect for dysfunctional attitudes in the pilot and current studies could be due to a number of methodological issues such as the measure used, the multiple presentations of the DAS, and the criteria used to select participants. For example, several studies have indicated that the instrument used to measure neuroticism and anxiety traits may play a role in conflicting findings of an association between the 5-HTTLPR and neuroticism and

anxiety (Munafo, Clark, & Flint, 2005; Schinka, 2005; Schmitz, Hennig, Kuepper, & Reuter, 2007). Similar effects could impact the measurement of negative thinking in general and dysfunctional attitudes in particular.

In addition, a lack of a reliable association between 5-HTTLPR and dysfunctional attitudes may arise due to the complex nature of constructs such as "dysfunctional attitudes" with a single gene likely contributing only a small amount of the overall variance between individuals (Kendler, 2005). For example, in the pilot study the interaction between genotype and time accounted for less than 1 percent of the variance in change in dysfunctional attitudes. In the current study, the interaction accounted for approximately 2% of the variance in the full sample and almost 4% in the Caucasian sample. Very large samples may be needed to reliably detect the effects of a single gene on such complex constructs.

Another mechanism that may contribute to the lack of consistency across studies is epistatic – that is, non-additive – gene-gene interactions. Unevenly distributed unmeasured genes could have epistatic relationships with the 5-HTTLPR and impact the results of these behavioral genetic studies. Several such epistatic interactions involving the 5-HTTLPR have been found (e.g., Hranilovic, Stefulj, Schwab, Borrmann-Hassenbach, Albus, Jernej, et al., 2004; Pezawas, Meyer-Lindenberg, Goldman, Verchinski, Chen, Kolachana, et al., 2008; Prasad, Zhu, McCauley, Samuvel, Ramamoorthy, Shelton, et al., 2005). Specifically, the epistatic interaction between the 5-HTTLPR and the brain-derived neurotrophic factor (BDNF) Val66Met polymorphisms may be particularly relevant.

In humans, the 5-HTTLPR *s* allele is associated with decreased amygdala and anterior cingulate volume compared to long allele homozygotes (Pezawas et al., 2005). However, the presence of the BDNF Met allele protects against the structural volume reduction associated with the 5-HTTLPR *s* allele (Pezawas et al., 2008). The expected

reduction in amygdala and anterior cingulate volume is observed in individuals with BDNF Val/Val genotype with the *s* allele, but is absent in individuals with Val/Met genotype and the *s* allele. Thus, the BDNF Met allele alters the functioning of the short allele of the 5-HTTLPR.

In fact, reanalyzing the association between the 5-HTTLPR and dysfunctional attitudes in the pilot study including BDNF genotype revealed a significant interaction between the genes on dysfunctional attitudes. Namely, the *ss* 5-HTTLPR genotype group demonstrated a significant increase in dysfunctional attitudes after the sad mood induction, but only when the participants were also homozygous for the Val BDNF allele (Wells, Beevers, & McGeary, in press). Consistent with findings in brain volume reduction by Pezawas and colleagues (2008), the BDNF Met allele protected against the effects of the 5-HTTLPR short allele. As the BDNF was not a focus of the current study, BDNF genotype and its interaction with 5-HTTLPR genotype have not been conducted. However, future analyses may investigate the interaction between 5-HTTLPR and other genetic variants (including the BDNF) on the outcomes reported in the current study. Regardless, future research should investigate the effects of potential gene-gene interactions on behavioral and cognitive variables.

### 6.1.2 Attention Bias and 5-HTTLPR Variation

In the pilot study, there was a significant association between 5-HTTLPR variation and change in bias for happy faces, but there was not a significant association with change in bias for sad faces. In the full sample, the current study did not reveal a significant interaction between genotype, mood induction condition, and attention bias. Thus, Hypotheses I and II were not supported in the full sample. However, there was a significant main effect for mood induction condition with participants showing increased bias for both happy and sad emotional faces (compared to neutral faces) in the sad mood condition.

In the Caucasian sample, there was a significant interaction between 5-HTTLPR status and mood induction condition. Specifically, the *ss* group showed increased bias towards emotional faces (compared to neutral faces) after the sad mood induction. Because there were no interactions with stimulus type, these analyses collapsed bias for both happy and sad stimuli into one variable. Therefore, Hypotheses I was not supported in the Caucasian sample, and II was partially supported in that the *ss* group demonstrated increased bias for emotional stimuli in the sad mood induction condition.

The current study found increased bias for emotional faces compared to neutral faces in the ss genotype group regardless of the valence of the emotional face. Previous research using an exogenous cuing task found similar results in two independent samples with short allele-carriers demonstrating difficulty disengaging from emotional faces (happy, sad, and fearful) regardless of valence (Beevers, Wells, et al., 2009). These data are consistent with neuroimaging studies demonstrating increased amygdala activation to emotional information regardless of valence in short allele-carriers (Dannlowski, Ohrmann, Bauer, Deckert, Hohoff, Kugel, et al., 2008; Munafo et al., 2008). Together, the selective attention data and the fMRI data suggest that the short allele may be related to enhanced reactivity to emotional stimuli in general rather than to negative emotional stimuli in particular.

These data fit well with the interpretation of the 5-HTTLPR as a "plasticity" gene rather than simply a vulnerability gene. The plasticity gene hypothesis posits that the short allele of the 5-HTTLPR may be associated with a broad, increased susceptibility to environmental influence rather than a particular vulnerability to psychopathology (Belsky, Jonassaint, Pluess, Stanton, Brummett, & Williams, 2009). In the current study, this increased susceptibility to environmental influence is exemplified in the increase in bias for emotional faces after a sad mood induction. That is, when induced into a sad mood, the short allele was associated with increased attention to the contextually-relevant

environmental stimuli (emotional faces) compared to the less relevant stimuli (non-emotional neutral faces).

However, it should be noted that the majority of previous published studies have shown a relationship between 5-HTTLPR status and attention for emotional material with a particular valence. For example, in a number of studies, the short allele is associated with increased bias for negatively valenced stimuli (Beevers, Gibb, et al., 2007; Osinsky, Reuter, Kupper, Schmitz, Kozyra, Alexander, et al., 2008; Perez-Edgar, Bar-Haim, McDermott, Gorodetsky, Hodgkinson, Goldman, et al., 2010). In contrast, a study using eye-tracking found that short allele homozygotes displayed selective attention for *positive* image stimuli presented for longer (30 s) durations (Beevers, Ellis, Wells, & McGeary, 2010). Others have found that the long allele is associated with a bias toward positive stimuli (Fox, Ridgewell, & Ashwin, 2009; Perez-Edgar et al., 2010) or away from negative stimuli (Fox et al., 2010; Kwang, Wells, McGeary, Swann, & Beevers, in press) that is absent or reduced with short alleles. Differences in tasks used, participant selection, stimuli presented, and other methodological factors may contribute to the disparate findings between association studies of the 5-HTTLPR and selective attention for emotional information. Replication of findings using similar samples, tasks, and stimuli will help elucidate the relationship between 5-HTTLPR variation and attention bias. In addition, carefully assessing environmental factors posited to moderate or mediate the effects of the 5-HTTLPR (e.g., life stress, current mood, past psychopathology) may also help develop a more accurate and reliable model of genetic contributions to selective attention for emotional information.

### 6.1.3 Memory Bias and 5-HTTLPR Variation

The current study revealed no significant association between 5-HTTLPR variation and memory for emotional faces. Previous research suggests that the short allele is associated with poorer memory performance in both rats and humans (O'Hara et

al., 2007; Olivier et al., 2009). Although, at least one study has found that the *ss* genotype is associated with better memory performance than the *ll* genotype (Roiser et al., 2007). Only one previous study examined the impact of 5-HTTLPR variation on memory for emotional material and found that the *ss* genotype group demonstrated poorer recall of positive words than the ll group, but only after an acute tryptophan depletion (ATD) procedure (Firk & Markus, 2009). Future studies should examine memory for a variety of emotional material in various contexts (e.g., before and after ADT) to clarify the association (if any) between 5-HTTLPR variation and emotional memory.

### 6.2 Methodological Strengths and Weaknesses

The current study included a number of methodological strengths. For example, common factors that might impact reaction time or reaction time standard deviation in a college student sample – amount of sleep the previous night, sleepiness, number of alcoholic drinks consumed the previous night – were assessed. These factors were not significantly associated with reaction time or reaction time standard deviation and did not differ between genetic groups. In addition, the sample size was larger than many previous studies examining the association between the 5-HTTLPR and cognitive aspects of depression. I also used a comprehensive structured clinical interview to determine whether participants were psychiatrically healthy, and this was one of the only studies to rigorously exclude participants with current or past psychopathology. Thus, the impact of psychopathology as an unaccounted third variable is reduced if not eliminated. Furthermore, in the current study, the assessments of dysfunctional attitudes and attention bias were administered at least a day apart and the order of the mood induction was counterbalanced. This allowed for the assessment of order effects for the mood induction and reduced the impact of potential priming effects of repeating the cognitive assessments.

The results should also be interpreted with a number of limitations in mind. First, although the sample size was relatively large compared to other studies examining the association between the 5-HTTLPR and cognitive aspects of depression, the sample size was relatively small compared to modern genetic association study standards, which often include several hundred to several thousand participants. In addition, the sample was comprised entirely of healthy young adults enrolled at the University of Texas. Individuals who have reached their late teens and early twenties without experiencing a depressive episode may differ genetically from individuals who have an earlier age-at-onset as previous research has demonstrated a higher genetic loading for early-onset depression than late-onset depression (Lyons, Eisen, Goldberg, True, Lin, Meyer, et al., 1998). Therefore, the current sample may represent individuals who, by virtue of genetic or environmental factors, are particularly resilient to depression. Thus, the association between 5-HTTLPR variability and vulnerability to depression may be particularly weak in the current sample.

### 6.3 Future Directions

Future studies should recruit larger samples to allow statistical testing with appropriate power in each racial group. This will help control for effects of population stratification and allow for greater power to detect smaller genetic effects. Another way to increase statistical power is to examine more "upstream" processes such as differences in brain structure and function. For example, the association between the 5-HTTLPR and amygdala activation in response to emotional images appears more robust than the association between 5-HTTLPR and depression in the context of life stress (Munafo, Brown, & Hariri, 2008; Risch et al., 2009). Examining such neural processes as intermediate phenotypes may provide more consistent results. Then, examining the relationship between neural structure and functioning and depression and depression-

related processes will help build a more comprehensive model of depression vulnerability.

In addition, future association studies should examine multiple genes. As mentioned above, epistatic interactions may explain some of the inconsistencies in genetic association studies. Developing a weighted genetic "risk score" for depression vulnerability from a number of different genes would likely provide a more comprehensive and accurate genetic assessment of risk. Such genetic risk scores have been developed and tested for a number of medical disorders such as multiple sclerosis and type 2 diabetes and provide a better assessment of risk than single genes (De Jager, Chibnik, Cui, Reischl, Lehr, Simon, et al., 2009; Meigs, Shrader, Sullivan, McAteer, Fox, Dupuis, et al., 2008).

As mentioned above, genetic loading for depression appears to vary based on age of onset with earlier age of onset associated with greater genetic loading (Lyons et al., 1998). Some of the most compelling recent evidence for a 5-HTTLPR by environment interaction involves participants younger than 15 years (e.g., Gibb, Benas, Grassia, & McGeary, 2009; Gibb, Uhrlass, Grassia, Benas, & McGeary, 2009; Gotlib, Joormann, Minor, & Hallmayer, 2008). In addition, approximately 20% of 18-year-olds have experienced at least one episode of depression (Hankin, Abramson, Moffitt, Silva, McGee, & Angell, 1998). Thus, excluding for a past history of depression reduces the available sample by 20% and excludes those individuals that may be most vulnerable to depression. In contrast, recruiting participants younger than 15 would eliminate only approximately 5% of the available sample due to a previous depressive episode (Hankin et al., 1998). Therefore, future studies examining 5-HTTLPR variation and depression vulnerability should recruit younger psychiatrically healthy samples or include and control for depression history in older samples.

As mentioned briefly above, genetic models of psychopathology are evolving beyond focusing almost exclusively on vulnerability and are beginning to focus on *plasticity*. Rather than viewing variants such as the 5-HTTLPR as markers of vulnerability, they are seen as markers of plasticity or susceptibility to environmental influence, whether good or bad (Belsky, Jonassaint, Pluess, Stanton, Brummett, & Williams, 2009). Future research should examine this hypothesis by not only examining the association between 5-HTTLPR and outcomes of interest in the context of stress or a sad mood, but also in the context of rewards and positive events. Such studies will be necessary to more fully understand the impact of 5-HTTLPR variation on human cognition and behavior.

### 6.4 Summary and Conclusions

Understanding the contributions of both genetic and cognitive factors to depression vulnerability is important for developing a more comprehensive model of the pathogenesis and maintenance of depression. The current study and pilot study investigated the relationship between 5-HTTLPR variation and cognitive reactivity of dysfunctional attitudes and attention bias for emotional information. Neither the pilot study nor the current study found a significant relationship between 5-HTTLPR variation and dysfunctional attitudes, but in each study the effects were in the expected direction. Variation of a single polymorphism likely explains only a small amount of the variance of a complex construct such as dysfunctional attitudes. Future studies should recruit larger samples and investigate the potential impact of other genes such as the BDNF gene (see, for example, Wells, Beevers, & McGeary, in press).

The current study did find a significant association between 5-HTTLPR variation and cognitive reactivity of attention bias for emotional information. Specifically, the short allele was associated with increased attention bias for emotional (i.e. happy and sad) faces after a sad mood induction compared to after a neutral mood induction. These

data are consistent with previous research using an exogenous cuing task (Beevers, Wells, et al., 2009) and with neuroimaging studies showing increased amygdala activation in response to emotional information in individuals with short alleles (Munafo et al., 2008). However the findings are in contrast to the pilot study findings and other previous research demonstrating an association between the short allele and attention bias for emotional stimuli of a particular valence (e.g., Beevers, Gibb, et al., 2007; Fox et al., 2010). Future research should examine potential moderating and mediating factors to better understand this relationship.

Nevertheless, the current study and the pilot study contribute to a now considerable body of research demonstrating a relationship between 5-HTTLPR variation and attention for emotional information. Selective attention for emotional information is hypothesized to be important for the etiology and maintenance of major depression (e.g., Beevers, 2005; Teasdale, 1988) and there is growing empirical evidence supporting these hypotheses (e.g., Beevers & Carver, 2003; Wells & Beevers, in press). Thus, the studies demonstrating the effects of 5-HTTLPR variation on attention bias for emotional information may describe one mechanism by which the 5-HTTLPR contributes to depression vulnerability. It will be important for future research to continue to examine the relationships between genetic, neural, and cognitive factors to construct a more comprehensive model of depression vulnerability.

# Appendix: Self-Report Measures

**Demographic Information**

To start with, we would like to get some background information from you.

1. What is your age? _____ 2. What is your gender? _____ 3. What is your date of birth? _____ / _____ / _____

4. What is your current marital situation (please check one)?

_____ Married _____ Separated _____ Never married/Single
_____ Common law marriage _____ Divorced _____ Widowed

5. Do you consider yourself to be Hispanic or Latino (see definition below)? ☐ Yes ☐ No

***Hispanic or Latino.*** A person of Mexican, Puerto Rican, Cuban, South or Central American, or other Spanish culture or origin, regardless of race.

6. What is your race? (please check one)

| | | |
|---|---|---|
| ☐ | American Indian or Alaska Native | A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment. |
| ☐ | Asian | A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. |
| ☐ | Black or African American | A person having origins in any of the black racial groups of Africa. |
| ☐ | Native Hawaiian or Other Pacific Islander | A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. |
| ☐ | White | A person having origins in any of the original peoples of Europe, the Middle East, or North Africa. |
| ☐ | Multiple races | |
| ☐ | None of the above | |

7. What is the highest grade in school you have completed (please check one)?

_____ Less than High School (**record actual grade**)
_____ High School
_____ 1 year of college or technical school
_____ 2 or more years of college but did not graduate
_____ A.A. or other degree that is not a B.A. or B.S.
_____ 4 years of college with degree
_____ Postgraduate, M.D., Ph.D.

8. How many people do you live with (not including yourself)?

_____ Number of children _____ Number of adults

9. During the past year, what was your total family income? $ _____

10. How many hours of sleep did you get last night? _____

11. How many hours of sleep do you get per night on average? _____

12. How tired (sleepy) are you today (circle one)? Not at all tired A little tired Moderately tired Very tired
13. How many alcoholic drinks did you have last night (1 drink = 12 oz. beer, 5 oz. wine, 1 oz./shot liquor)? _____

14. Do you ***currently*** take medication for emotional problems (e.g., anxiety, depression)? ☐ No ☐ Yes

If yes, please list below (if you need additional room, please continue on the back of this page):

| Date Prescribed | Medication name | Dosage | Reason for medication |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

15. ***In the past***, did you take any medication for emotional problems (e.g., anxiety, depress.)? ☐ No ☐ Yes

If yes, please list below (if you need additional room, please continue on the back of this page):

| Duration | Medication name | Dosage | Reason for medication |
|---|---|---|---|
| From to | | | |

| | | | |
|---|---|---|---|
| From to | | | |
| From to | | | |
| From to | | | |

16. Have you ever been in therapy or counseling for emotional problems? ☐ No ☐ Yes

If yes, please list below (if you need additional room, please continue on the back of this page):

| Duration | Type of provider (PhD, MD, priest, social worker) | # of sessions | Reason for therapy |
|---|---|---|---|
| From to | | | |
| From to | | | |
| From to | | | |

17. Have you ever been hospitalized for emotional problems (e.g., anxiety, depression, drugs)? ☐ No ☐ Yes

If yes, please list below (if you need additional room, please continue on the back of this page):

| Duration | Length of stay | Reason for hospitalization |
|---|---|---|
| From to | | |
| From to | | |
| From to | | |

18. Please list any family history of psychological/psychiatric illnesses (e.g., depression, anxiety, alcohol, drug)

| Person's Relationship to you (e.g., mother, paternal aunt, etc.) | Diagnosis/Problem(s) or Symptom(s) | Treatment Received? (Y/N) | Type of Treatment |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

19. Please list any personal current medical illnesses/concerns

| Diagnosis/Problem(s) or Symptom(s) | Onset? | Treatment Received? (Y/N) | Type of Treatment |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

**BDI-II**

This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the ONE STATEMENT in each group that bests describes the way you have been feeling during the PAST TWO WEEKS, INCLUDING TODAY. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in sleeping pattern) or Item 18 (Changes in Appetite).

**1. Sadness**

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time
3 I am so sad or unhappy that I can't stand it

**2. Pessimism**

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel that my future is hopeless and will only get worse.

**3. Past Failure**

0 I do not feel like a failure.
1 I have failed more I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

**4. Loss of Pleasure**

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

**5. Guilty Feelings**

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

**6. Punishment Feelings**

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

**7. Self-Dislike**

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

**8. Self-Criticalness**

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens

**9. Suicidal Thoughts or Wishes**

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

**10. Crying**

0 I don't cry any more than I used to.
1 I cry more than I used to
2 I cry over every little thing.
3 I feel like crying, but I can't.

**11. Agitation**

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

**12. Loss of Interest**

0 I have not lost interest in other people or activities
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things
3 It's hard to get interested in anything.

**13. Indecisiveness**

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

**14. Worthlessness**

0 I don't feel I am worthless.
1 I do not consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

**15. Loss of Energy**

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

**16. Changes in Sleeping Pattern**

0 I have not experienced any change in my sleeping pattern.

---

1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.

---

2a I sleep a lot more than usual.
2b I sleep a lot less than usual.

---

3a I sleep most of the day.
3b I wake up 1-2 hours early and can't get back to sleep.

**17. Irritability**

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

**18. Changes in Appetite**

0 I have not experienced any change in my appetite

---

1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.

---

2a My appetite is much less than before.
2b My appetite is much greater than usual.

---

3a I have no appetite at all.
3b I crave food all the time.

**19. Concentration Difficulty**

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

**20. Tiredness or Fatigue**

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

**21. Loss of interest in Sex**

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

**IDAS**

Below is a list of feelings, sensations, problems, and experiences that people sometimes have. Read each item to determine how well it describes your recent feelings and experiences. Then select the option that best describes **how much** you have felt or experienced things this way **during the past two weeks, including today.**

| | Not at all | A little bit | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|---|
| 1. I felt sad | 1 | 2 | 3 | 4 | 5 |
| 2. I did not have much of an appetite | 1 | 2 | 3 | 4 | 5 |
| 3. I had little interest in my usual hobbies and activities | 1 | 2 | 3 | 4 | 5 |
| 4. I felt optimistic | 1 | 2 | 3 | 4 | 5 |
| 5. I slept less than usual | 1 | 2 | 3 | 4 | 5 |
| 6. I worried a lot | 1 | 2 | 3 | 4 | 5 |
| 7. I felt fidgety, restless | 1 | 2 | 3 | 4 | 5 |
| 8. I felt exhausted | 1 | 2 | 3 | 4 | 5 |
| 9. I felt a pain in my chest | 1 | 2 | 3 | 4 | 5 |
| 10. I felt depressed | 1 | 2 | 3 | 4 | 5 |
| 11. I felt guilty | 1 | 2 | 3 | 4 | 5 |
| 12. I had trouble making up my mind | 1 | 2 | 3 | 4 | 5 |
| 13. I talked more quickly than was usual | 1 | 2 | 3 | 4 | 5 |
| 14. I was proud of myself | 1 | 2 | 3 | 4 | 5 |
| 15. I had trouble falling asleep | 1 | 2 | 3 | 4 | 5 |
| 16. I was furious | 1 | 2 | 3 | 4 | 5 |

| | How much have you felt or experienced this over the past two weeks? | Not at all | A little bit | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|---|---|
| 17. | I had thoughts of suicide | 1 | 2 | 3 | 4 | 5 |
| 18. | I had disturbing thoughts of something bad that happened to me | 1 | 2 | 3 | 4 | 5 |
| 19. | I felt self-conscious knowing that others were watching me | 1 | 2 | 3 | 4 | 5 |
| 20. | I did not enjoy things that I usually like | 1 | 2 | 3 | 4 | 5 |
| 21. | I felt useless | 1 | 2 | 3 | 4 | 5 |
| 22. | I felt dizzy or lightheaded | 1 | 2 | 3 | 4 | 5 |
| 23. | I felt irritable | 1 | 2 | 3 | 4 | 5 |
| 24. | I woke up early and could not get back to sleep | 1 | 2 | 3 | 4 | 5 |
| 25. | I was worried about embarrassing myself socially | 1 | 2 | 3 | 4 | 5 |
| 26. | I thought a lot about food | 1 | 2 | 3 | 4 | 5 |
| 27. | I had trouble sitting still | 1 | 2 | 3 | 4 | 5 |
| 28. | I felt anxious | 1 | 2 | 3 | 4 | 5 |
| 29. | I felt too tired to do anything | 1 | 2 | 3 | 4 | 5 |
| 30. | I became anxious in a crowded public setting | 1 | 2 | 3 | 4 | 5 |
| 31. | I blamed myself for things | 1 | 2 | 3 | 4 | 5 |
| 32. | I worried about the future | 1 | 2 | 3 | 4 | 5 |
| 33. | I cut or burned myself on purpose | 1 | 2 | 3 | 4 | 5 |
| 34. | I felt that I had accomplished a lot | 1 | 2 | 3 | 4 | 5 |

| | How much have you felt or experienced this over the past two weeks? | Not at all | A little bit | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|---|---|
| 35. | I felt fearful | 1 | 2 | 3 | 4 | 5 |
| 36. | I ate when I wasn't hungry | 1 | 2 | 3 | 4 | 5 |
| 37. | I woke up much earlier than usual | 1 | 2 | 3 | 4 | 5 |
| 38. | I felt like eating less than usual | 1 | 2 | 3 | 4 | 5 |
| 39. | I looked forward to things with enjoyment | 1 | 2 | 3 | 4 | 5 |
| 40. | I had nightmares that reminded me of something bad that happened | 1 | 2 | 3 | 4 | 5 |
| 41. | I slept more than usual | 1 | 2 | 3 | 4 | 5 |
| 42. | It took a lot of effort for me to get going | 1 | 2 | 3 | 4 | 5 |
| 43. | I felt inadequate | 1 | 2 | 3 | 4 | 5 |
| 44. | I was trembling or shaking | 1 | 2 | 3 | 4 | 5 |
| 45. | I thought the world would be better off without me | 1 | 2 | 3 | 4 | 5 |
| 46. | I had memories of something scary that happened | 1 | 2 | 3 | 4 | 5 |
| 47. | I felt like breaking things | 1 | 2 | 3 | 4 | 5 |
| 48. | It was hard for me to find pleasure in things | 1 | 2 | 3 | 4 | 5 |
| 49. | I woke up frequently during the night | 1 | 2 | 3 | 4 | 5 |
| 50. | I felt enraged | 1 | 2 | 3 | 4 | 5 |
| 51. | I felt ashamed of things I had done | 1 | 2 | 3 | 4 | 5 |
| 52. | I hurt myself purposely | 1 | 2 | 3 | 4 | 5 |

| | How much have you felt or experienced this over the past two weeks? | Not at all | A little bit | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|---|---|
| 53. | I felt faint | 1 | 2 | 3 | 4 | 5 |
| 54. | I felt discouraged about things | 1 | 2 | 3 | 4 | 5 |
| 55. | I felt like throwing things | 1 | 2 | 3 | 4 | 5 |
| 56. | I found it difficult to make eye contact with people | 1 | 2 | 3 | 4 | 5 |
| 57. | My appetite was poor | 1 | 2 | 3 | 4 | 5 |
| 58. | I got upset thinking about something bad that had happened | 1 | 2 | 3 | 4 | 5 |
| 59. | I had trouble waking up in the morning | 1 | 2 | 3 | 4 | 5 |
| 60. | Everything seemed to take a lot of effort | 1 | 2 | 3 | 4 | 5 |
| 61. | I lost my temper and yelled at people | 1 | 2 | 3 | 4 | 5 |
| 62. | My heart was racing or pounding | 1 | 2 | 3 | 4 | 5 |
| 63. | I was told that I seem to be moving more slowly than usual | 1 | 2 | 3 | 4 | 5 |
| 64. | I felt confused | 1 | 2 | 3 | 4 | 5 |
| 65. | I thought about my own death | 1 | 2 | 3 | 4 | 5 |
| 66. | I found it difficult to talk with people I did not know well | 1 | 2 | 3 | 4 | 5 |
| 67. | I got annoyed easily | 1 | 2 | 3 | 4 | 5 |
| 68. | I found myself worrying all the time | 1 | 2 | 3 | 4 | 5 |
| 69. | I had a very dry mouth | 1 | 2 | 3 | 4 | 5 |
| 70. | I felt like crying | 1 | 2 | 3 | 4 | 5 |

| | How much have you felt or experienced this over the past two weeks? | Not at all | A little bit | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|---|---|
| 71. | I felt like eating more than usual | 1 | 2 | 3 | 4 | 5 |
| 72. | I felt hopeful about the future | 1 | 2 | 3 | 4 | 5 |
| 73. | I slept very poorly | 1 | 2 | 3 | 4 | 5 |
| 74. | I felt like a failure | 1 | 2 | 3 | 4 | 5 |
| 75. | I had trouble remembering things | 1 | 2 | 3 | 4 | 5 |
| 76. | I thought about hurting myself | 1 | 2 | 3 | 4 | 5 |
| 77. | I felt that I had a lot to look forward to | 1 | 2 | 3 | 4 | 5 |
| 78. | I felt grouchy | 1 | 2 | 3 | 4 | 5 |
| 79. | I felt much worse in the morning than later in the day | 1 | 2 | 3 | 4 | 5 |
| 80. | I felt angry | 1 | 2 | 3 | 4 | 5 |
| 81. | I felt inferior to others | 1 | 2 | 3 | 4 | 5 |
| 82. | I felt drowsy, sleepy | 1 | 2 | 3 | 4 | 5 |
| 83. | I was short of breath | 1 | 2 | 3 | 4 | 5 |
| 84. | I was told I seemed more restless than usual | 1 | 2 | 3 | 4 | 5 |
| 85. | I talked more slowly than usual | 1 | 2 | 3 | 4 | 5 |
| 86. | I felt tense | 1 | 2 | 3 | 4 | 5 |
| 87. | Nothing seemed interesting to me | 1 | 2 | 3 | 4 | 5 |
| 88. | I slept too much at times | 1 | 2 | 3 | 4 | 5 |

| | How much have you felt or experienced this over the past two weeks? | Not at all | A little bit | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|---|---|
| 89. | I felt like I was choking | 1 | 2 | 3 | 4 | 5 |
| 90. | I felt worn out | 1 | 2 | 3 | 4 | 5 |
| 91. | I felt unhappy | 1 | 2 | 3 | 4 | 5 |
| 92. | I felt like I had a lot of interesting things to do | 1 | 2 | 3 | 4 | 5 |
| 93. | It was hard for me to control my temper | 1 | 2 | 3 | 4 | 5 |
| 94. | I felt nervous | 1 | 2 | 3 | 4 | 5 |
| 95. | I did not feel like eating | 1 | 2 | 3 | 4 | 5 |
| 96. | I had trouble concentrating | 1 | 2 | 3 | 4 | 5 |
| 97. | Little things made me mad | 1 | 2 | 3 | 4 | 5 |
| 98. | I ate more often than usual | 1 | 2 | 3 | 4 | 5 |
| 99. | I felt like I had a lot of energy | 1 | 2 | 3 | 4 | 5 |

**$DAS_1$**

The sentences below describe people's attitudes. Circle the number which best describes how much each sentence describes your attitude. Your answer should describe the way you think most of the time.

| | **Attitudes:** Remember, choose your answers according to the way you think most of the time. | **Totally Agree** | **Agree Very Much** | **Agree Slightly** | **Neutral** | **Disagree Slightly** | **Disagree Very Much** | **Disagree Totally** |
|---|---|---|---|---|---|---|---|---|
| 1. | It is difficult to be happy unless one is good-looking, intelligent, rich and creative | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 2. | Happiness is more a matter of my attitude toward myself than the way other people feel about me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 3. | People will probably think less of me if I make a mistake | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 4. | If I do not do well all the time, people will not respect me | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 5. | Taking even a small risk is foolish because the loss is likely to be a disaster. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 6. | It is possible to gain another person's respect without being especially talented at anything. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 7. | I cannot be happy unless most people I know admire me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 8. | If a person asks for help, it is a sign of weakness. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 9. | If I do not do as well as other people, it means I am an inferior human being. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 10. | If I fail at my work, then I am a failure as a person. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 11. | If you cannot do something well, there is little point in doing it at all. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 12. | Making mistakes is fine because I can learn from them. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 13. | If someone disagrees with me, it probably indicates he does not like me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 14. | If I fail partly, it is as bad as being a complete failure. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 15. | If other people know what you are really like, they will think less of you. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 16. | I am nothing if a person I love doesn't love me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

| | **Attitudes:** Remember, choose your answers according to the way you think most of the time. | **Totally Agree** | **Agree Very Much** | **Agree Slightly** | **Neutral** | **Disagree Slightly** | **Disagree Very Much** | **Disagree Totally** |
|---|---|---|---|---|---|---|---|---|
| 17. | One can get pleasure from an activity regardless of the end result. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 18. | People should have a reasonable likelihood of success before undertaking anything. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 19. | My value as a person depends greatly on what others think of me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 20. | If I don't se the highest standards for my self, I am likely to end up a second-rate person. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 21. | If I am to be a worthwhile person, I must be truly outstanding in at least one major respect. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 22. | People who have good ideas are more worthy than those who do not. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 23. | I should be upset if I make a mistake. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 24. | My own opinions of myself are more important than other's opinions of me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 25. | To be a good, moral, worthwhile person, I must help everyone who needs it. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 26. | If I ask a question, it makes me look inferior. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 27. | It is awful to be disapproved of by people important to you. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 28. | If you don't have other people to lean on, you are bound to be sad. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 29. | I can reach important goals without slave driving myself. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 30. | It is possible for a person to be scolded and not get upset. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 31. | I cannot trust other people because they might be cruel to me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 32. | If others dislike you, you cannot be happy. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 33. | It is best to give up your own interests in order to please other people. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 34. | My happiness depends more on other people than it does on me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

| | **Attitudes:** Remember, choose your answers according to the way you think most of the time. | **Totally Agree** | **Agree Very Much** | **Agree Slightly** | **Neutral** | **Disagree Slightly** | **Disagree Very Much** | **Disagree Totally** |
|---|---|---|---|---|---|---|---|---|
| 35. | I do not need the approval of other people in order to be happy. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 36. | If a person avoids problems, the problems tend to go away. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 37. | I can be happy even if I miss out on many of the good things in life. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 38. | What other people think about me is very important. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 39. | Being isolated from others is bound to lead to unhappiness. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 40. | I can find happiness without being loved by another person. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

**$DAS_2$**

The sentences below describe people's attitudes. Circle the number which best describes how much each sentence describes your attitude. Your answer should describe the way you think most of the time.

| | **Attitudes:** Remember, choose your answers according to the way you think most of the time. | **Totally Agree** | **Agree Very Much** | **Agree Slightly** | **Neutral** | **Disagree Slightly** | **Disagree Very Much** | **Disagree Totally** |
|---|---|---|---|---|---|---|---|---|
| 1. | You can be a happy person without going out of your way in order to please other people. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 2. | I have to impress new acquaintances with my charm, intelligence, or wit or they won't like me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 3. | If I put other peoples' needs before my own, they should help me when I want them to do something for me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 4. | It is shameful for someone to display his weakness. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 5. | People will like me even if I am not successful. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 6 | People who have the marks of success (good looks, fame, wealth) are bound to be happier than people who do not. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 7. | I should try to impress other people if I want them to like me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 8. | If a person I love does not love me, it means I am unlovable. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 9. | I ought to be able to solve my problems quickly and without a great deal of effort. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 10. | If a person is indifferent to me, it means he does not like me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 11. | I should be able to please everybody. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 12. | Others can care for me even if they know all my weaknesses. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 13. | If people whom I care about do not care for me, it is awful. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 14. | Criticism need not upset the person who receives the criticism. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 15. | My life is wasted unless I am a success. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 16. | People should prepare for the worst or they will be disappointed. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

| | **Attitudes:** Remember, choose your answers according to the way you think most of the time. | **Totally Agree** | **Agree Very Much** | **Agree Slightly** | **Neutral** | **Disagree Slightly** | **Disagree Very Much** | **Disagree Totally** |
|---|---|---|---|---|---|---|---|---|
| 17. | I must be a useful, productive, creative person or life has no purpose. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 18. | A person should think less of himself if other people do not accept him. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 19. | I do not need other people's approval for me to be happy. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 20. | I can enjoy myself even when others do not like me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 21. | My value as a person depends greatly on what others think of me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 22. | If I make a foolish statement, it means I am a foolish person. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 23. | If a person has to be alone for a long period of time, it follows that he has to feel lonely. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 24. | A person should be able to control what happens to him. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 25. | If a person is not a success, then his life is meaningless. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 26. | A person doesn't need to be well liked in order to be happy. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 27. | If someone performs a selfish act, this means he is a selfish person. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 28. | I should always have complete control over my feelings. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 29. | I should be happy all the time. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 30. | If people consider me unattractive it need not upset me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 31. | Whenever I take a chance or risk I am only looking for trouble. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 32. | A person cannot change his emotional reactions even if he knows they are harmful to him. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 33. | I may be able to influence other people's behavior but I cannot control it. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 34. | People will reject you if they know your weaknesses. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

| | **Attitudes:** Remember, choose your answers according to the way you think most of the time. | **Totally Agree** | **Agree Very Much** | **Agree Slightly** | **Neutral** | **Disagree Slightly** | **Disagree Very Much** | **Disagree Totally** |
|---|---|---|---|---|---|---|---|---|
| 35. | People should be criticized for their weaknesses. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 36. | One should look for a practical solution to problems rather than a perfect solution. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 37. | If I do well, it probably is due to chance; if I do badly, it is probably my own fault. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 38. | The way to get people to like you is to impress them with your personality. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 39. | Turning to someone else for advice or help is an admission of weaknesses. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 40. | A person should do well at everything he undertakes. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

**PHQ**

For the *two weeks* in your life when you felt the *most* blue, sad, or depressed, how often were you bothered by any of the following problems?

| | Rarely/ Not at all | Several days | More than half the days | Nearly every day |
|---|---|---|---|---|
| 1. Little pleasure or interest in doing things | 0 | 1 | 2 | 3 |
| 2. Feeling down, depressed or hopeless | 0 | 1 | 2 | 3 |
| 3. Trouble falling or staying asleep or sleeping too much | 0 | 1 | 2 | 3 |
| 4. Feeling tired or having little energy | 0 | 1 | 2 | 3 |
| 5. Poor appetite or overeating | 0 | 1 | 2 | 3 |
| 6. Feeling bad about yourself – or that you are a failure or you have let yourself or your family down | 0 | 1 | 2 | 3 |
| 7. Trouble concentrating on things, such as reading the newspaper or watching television | 0 | 1 | 2 | 3 |
| 8. Moving or speaking slowly so that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual | 0 | 1 | 2 | 3 |
| 9. Thoughts that you would be better off dead, or of hurting yourself in some way | 0 | 1 | 2 | 3 |

| | Not at all | Somewhat | Very | Extremely |
|---|---|---|---|---|
| 10. How difficult did these problems make it for you to do your work, take care of things at home, or get along with other people? | 0 | 1 | 2 | 3 |

**AAL**

Below is a list of words that describe feelings people have. Please read each one carefully. Then circle one answer to the right which best describes how much you are feeling that way **RIGHT NOW**.

| | Not at all | A little | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|---|
| 1. Happy | 0 | 1 | 2 | 3 | 4 |
| 2. Worthless | 0 | 1 | 2 | 3 | 4 |
| 3. Sad | 0 | 1 | 2 | 3 | 4 |
| 4. Cheerful | 0 | 1 | 2 | 3 | 4 |
| 5. Pleasant | 0 | 1 | 2 | 3 | 4 |
| 6. Blue | 0 | 1 | 2 | 3 | 4 |
| 7. Hopeless | 0 | 1 | 2 | 3 | 4 |
| 8. Joyful | 0 | 1 | 2 | 3 | 4 |

**SIS (computer administered)**

1. How sad are you right now?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| Not at all | | | | | | | | Extremely |

2. How happy are you right now?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| Not at all | | | | | | | | Extremely |

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